

EXHIBIT 26

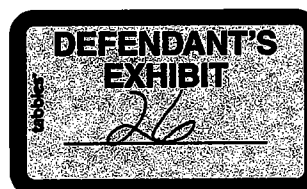
**Statistical Analysis of
Stability and Capability of the
Production Process for Digitek Doses 0.125mg and 0.25mg**

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Executive Summary

It is concluded that the Digitek manufacturing process was stable and capable during the 2003-2008 time period, including the production of Batch 70924A, and was consistently producing product that met specifications. No systematic or chronic manufacturing problems were identified. The statistical studies that support this conclusion are detailed in this report.

Batch Trends Analysis 2003 – 2008 Doses 0.125mg and 0.25mg

- The batch trend analysis supports the conclusion that the manufacturing process was stable for the 2003 - 2008 time periods. The year-to-year differences in annual averages for Blend assay (Avg), Blend assay uniformity, Tablet weight, hardness, thickness, assay and content uniformity were small and of no practical significance.
- The consistency of the performance of the production processes for the 0.125mg and 0.25mg Doses is very strong evidence that the Digitek production process was stable and capable during the time the data were collected. This is a large study covering 5 years of production involving approximately 500 batches of product.

Batch 70924A Production Data

- The API content was uniformly distributed throughout the blend.
- No double-thick tablets were detected by analysis of the in-process sampling data on tablet weight and thickness for Batch 70924A. All weight and thickness values were within specifications and no trends were detected. This indicates that the presence of the double-thick tablets was an isolated event and not due to a systematic or chronic manufacturing problem.
- The manufacturing process was stable throughout the production of Batch 70924A. No significant trends, shifts or cycles were detected.
- No out-of-specification results were found during manufacturing indicating that the process is capable of meeting specifications.
- The analysis of the in-process data collected independently by the operators and QA arrive at the same findings strengthening the conclusion that the production process is stable and capable. This agreement of results also provides evidence of the integrity of the data collection process.
- Differences in average values of the product parameters (tablet weight, hardness, thickness, assay and content uniformity) due to Press (#67 vs. #71) and Location on press (Front vs. Rear) are very small and of no practical significance.
- A comparison of the process and capability statistics for Batch 70924A with statistics of Batches 70836A and 70925A, which were manufactured, respectively, immediately before and after Batch 70924A, indicated that the process was stable and capable before, during and after the production of Batch 70924A.

Analysis of Batches 70836A, 70925A, 70207A, 70770A and 80228A

- Analysis of the blend, compression and content uniformity test data for Batches 70836A and 70925A, which were manufactured, respectively, immediately before and after Batch

70924A, identified no out of specification (OOS) results. This indicates that both batches were well within specifications. The production process was also found to be stable and capable during the manufacture of these batches providing additional evidence of the credible performance of the manufacturing process during the time period of the manufacture of Batch 70924A.

- Analysis of the test data for Batches 70207A and 70770A showed that, although some OOS results were observed for blend uniformity, it was appropriate to release the product. All of the blend uniformity acceptance values were within specifications.
- Analysis of the tablet weight data for Batch 80228A showed there were no significant trends in the tablet weight data indicating that the out-of-specification bottles and associated tablets were due to an isolated event and not due to any systematic or chronic production problems.
- A comparison of production test data for Batches 70836A, 70924A and 70925A was made to similar data from eight validation batches manufactured in 1994 and 1996. The analysis showed that there was no significant difference between the validation batches and the production batches indicating that the process that produced these three batches had the same performance as the process that was validated in 1994 and 1996.

Third Party Studies

- The analysis of the FDA 484 Sampling content uniformity data found that all tablet content uniformity relative standard deviation (RSD) values were within specification. There were no significant differences among the Actavis RSD values, or among the RSD values of the FDA 484 Samples. A comparison of the Actavis and FDA 484 Sampling RSD values found no significant differences between the RSD values of the Actavis and 484 Samples. It is concluded that the API content of the tablets in the batches sampled was uniform.
- The analysis by third party labs showed that the 0.125mg and 0.25mg doses were stable for Tablet assay and Tablet dissolution (the only parameters tested) over the 36 month time period tested. Three batches tested for tablet assay (% of label), content uniformity and dissolution found all three tablet parameters to be within specification.

Background

The analysis and conclusions discussed in this report are based on the following background:

1. The "Process Validation" documents (0.125mg and 0.25mg doses) submitted to the FDA in 1994-95, 96 verified the formula and process for manufacturing and testing of the product.
2. Each batch uses the formula and instructions for mixing, blending, compressing and packaging that were submitted to the FDA. Each step in the process is verified by sampling and testing by the QA organization and verified in the batch record documents. One change was made to reflect the actual assay amount and submitted to the FDA.

3. Quantic reviewed the batch records for 19 (0.125mg, 10 batches; 0.25mg, 9 batches) of the 152 recalled batches (0.125mg, 83 batches; 0.25mg, 69 batches) and found no problems. This is an important finding as 15.2% sample (19/152) is a very effective sample size that would detect a 10% “suspect batch” (out-of-spec results or standard operating procedures (SOPs) not followed) rate among the recalled batches with approximately 90% probability. In other words there is a high probability (approximately 90%) that a sample of 19 batches would detect a 10% suspect batch rate if it existed.
4. No data integrity issues have been identified. The process data documents are solid having been examined by FDA many times with no problems being identified.
5. All distributed recalled batches passed all tests that were made at all steps in the production process; blending, compression and chemical assay of tablets. Sampling was uniformly distributed across the manufacture of each batch; every 30 minutes by process operators and hourly by Quality Assurance (QA).
6. Third Party Testing and Reviewing – Actavis’ test results were supported by outside testing labs: Quantic (batch record review), FDA (tested 6 batches sampled at pharmacies and warehouses) and UDL. There were no problems identified by the test results of the different organizations. A total of 41 batches were tested by these organizations: Quantic (19 batches), Third party labs (11 batches), and FDA (11 batches). This testing covered 38 separate batches as 6 batches were tested by more than one organization.

This testing rate of 25% (38/152) is a very effective sample size that would detect a 10% “suspect batch” (out-of-spec results or standard operating procedures (SOPs) not followed) rate among the recalled batches with approximately 99% probability. In other words, there is a high probability (approximately 99%) that a sample of 38 batches would detect a 10% problem batch rate if it existed. The finding of no problems in a sample of 38 batches adds further evidence of the lack of problems with the Digitek product.

FDA, through its 484 Sampling Program, tested 11 batches for tablet content uniformity (doses 0.125mg and 0.25mg) and found content uniformity RSD values to be well within specifications.

Third party labs performed stability testing for Tablet assay and dissolution (0, 3, 6, 9, 12, 18, 24 and 36 months) of 33 samples (Doses 0.125mg and 0.25mg). Both doses showed no Tablet assay or Tablet dissolution problems.

7. The product recall was based on finding double-thick tablets in Batch 70924A. Five double-thick tablets were found during packaging. Fifteen double-thick tablets were found during a subsequent 100% inspection. Harm to patients was unlikely as the double-thick tablets found in this batch was very small and no double-thick tablets have been found outside the manufacturing facility in any part of the distribution channel including pharmacies and observation by consumers (FDA July 2009). Double-thick tablets are easy to detect as they are twice the size of the normal tablets. Many of prescriptions filled by pharmacies, including those in hospitals, are counted by hand and the tablets are individually observed. One double-thick tablet was found by a pharmacist in 2004.

8. Many of the tests done on tablets result in tablets being destroyed. As a result, it is standard practice to use sampling to verify the product meets specifications. FDA approved sampling was done every 30 minutes by the process operators and hourly by the QA organization. Batch 70924A passed all the routine QA tests.

Study Description and Objective

The background described above and all of the tests done on the product have identified no problems; all released product met specifications. Such results could only happen if the production process was performing well.

Manufacturing processes that are “Stable and Capable” over time can be expected to consistently produce product that is within specifications and thereby cause no harm to patients due to nonconforming product. Stability and capability are described as follows:

- **A Stable manufacturing process** is a process that is in a state of statistical control as each batch of tablets is being produced and as batches of tablets are produced over time. A process in a state of statistical control consistently produces product that varies within the process control limits; typically set at the process average (X-Bar) plus and minus three standard deviations (SD) of the process variation for the parameter of interest.

$$\text{Lower Control Limit} = \text{Process Average} - 3(\text{SD})$$

$$\text{Upper Control Limit} = \text{Process Average} + 3(\text{SD})$$

Separate control limits are set for each parameter e.g.; tablet thickness, hardness and thickness. Any sample value that is outside of these limits is an indication that the process may not be in a state of statistical control.

- **A Capable manufacturing process** is one that consistently produces tablets that are within specifications for all tablet parameters. A process capability analysis compares the process variation to the lower and upper specification limits for the product. A broadly used measure of process capability is the Ppk index which is discussed further in the Statistical Methods section.

These concepts can be illustrated by a hypothetical example. A process may be producing tablets with an average hardness of 4.0kp and a standard deviation of 0.3kp. The control limits would be $4.0 \pm 3(0.3)$ for a range of 3.1 – 4.9. Any tablet outside of the 3.1 – 4.9 range would be an indication that the process average may have changed and a process adjustment may be needed. A hardness value of 5.2kp would be such an indication; however in this example, the tablet is acceptable as the hardness specifications are 1-6kp.

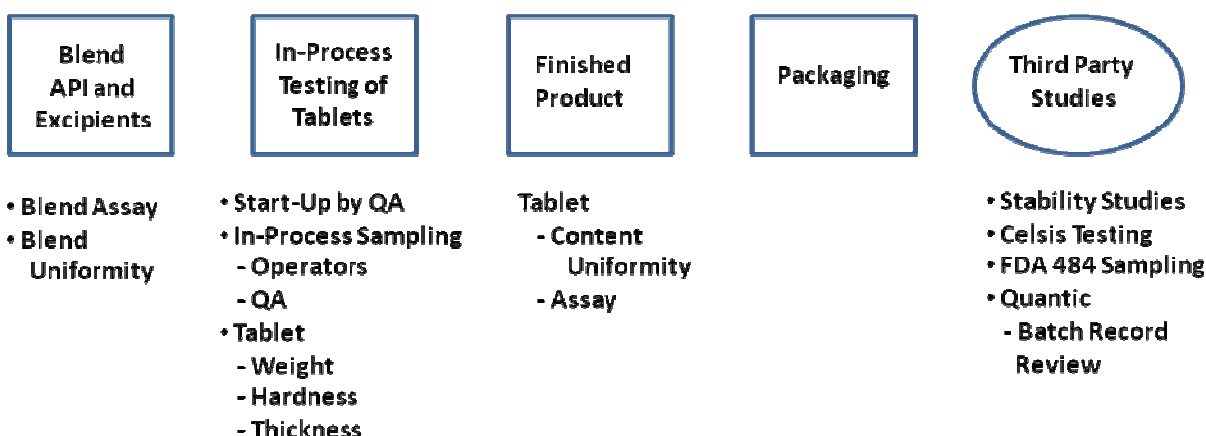
A production process can be in any one of the four combinations of Stability and Capability: Stable and Capable (desired state), Stable and Not Capable, Not Stable and Capable and Not Stable and Not Capable (worst possible situation).

Control Limits and Specification Limits. It is important to understand the difference between process control limits and product specification limits.

- **Control limits** apply to the process. Control limits are used to assess the stability of the process and suggest process adjustments when the out of control samples are detected.
- **Specification limits** apply to the product and are used to assess the capability of the process to produce product that has the desired properties and characteristics.

The objective of this study is to analyze the available production data to assess and measure the stability and capability of the Digitek production process. All analyses were done using the Minitab 16 statistical analysis and Microsoft Excel software packages.

Process Measurements Analyzed



Description of Data Sources

The data and information used in this study are from the following sources:

- Data on 496 batches contained in Annual Product Reviews 2003-2008 for doses 0.125mg and 0.25mg. Specifically for each batch produced:
 - Blend assay – Average and relative standard deviation (RSD)
 - Tablet weight – Average and standard deviation
 - Tablet hardness – Average and standard deviation
 - Tablet thickness – Average and standard deviation
 - Tablet content uniformity – Relative standard deviation (RSD)
 - Assay (% of Label)
- Data contained in production and QA records for batch 70924A on Tablet Presses #67 and #71 with Front and Rear tablet exit chute locations on each press.
 - QA blend content uniformity
 - QA Start-Up – Tablet weight, hardness and thickness
 - QA In-Process sampling – Tablet weight, hardness and thickness
 - Operator In-Process sampling – Tablet weight, hardness and thickness
 - QA tablet content uniformity

- Eleven validation batches manufactured in 1994, 1995 and 1996
- Quantic batch record review
- FDA 484 Sampling data on tablet content uniformity for 0.125mg and 0.25mg doses
- Third Party Stability Test results for Tablet assay and dissolution - Defendant's Exhibits 83 and 84

Approach

The data described above enable the following studies to be done:

- 1) Analyze the data from the annual review reports to assess process stability and capability over the five year period 2003 – 2008.
- 2) Analyze the production and QA data collected on Batch 70924A to assess process stability and capability and product quality during the production of this batch. Batches 70836A and 70925A produced immediately before and after Batch 70924A were also evaluated.
- 3) Analyze data from third party studies to further evaluate the stability and capability of the Digitek production process.

Collectively these analyses will enable us to determine whether the Digitek manufacturing process has the ability to consistently produce product that meets specifications. The statistical methods used to perform these analyses are described in the following section.

Statistical Methods Used

Introduction

The statistical methods used in this work are generally accepted methods for assessing the stability and capability of a process over time and are well documented in the statistical literature (Montgomery 2009, Conover 1999). As a general principle, it is a very rare event that a manufacturing process that is stable and capable will produce a product that is out of specifications. The overall strategy of this analysis is to answer the question: Is the Digitek manufacturing process capable of consistently producing product that is within specifications over time? The statistical analyses conducted to answer this question are briefly described below. The associated calculations were completed using the Minitab Version 16 statistical software.

Control Chart Analysis

A control chart analysis was used to assess the stability of a process over time. Standard **Shewhart control chart analysis** methods were used throughout this analysis. The Shewhart chart has been a widely used globally as a tool to assess process stability since the 1930's. X-Bar and Standard Deviation charts were used when more than one observation (e.g.; >1 tablet) was present for each sample. Individual-Moving Range charts were used when only one measurement was made at each sampling point.

A **stable process** is a predictable process; a process whose product will vary within a stated set of limits, called control limits. A stable process is sometimes referred to as being in a state of statistical control.

A stable process has no sources of **special cause variation** – effects of variables that are outside the process but yet have an effect on the performance of the process (e.g., process operators, ambient temperature and humidity, raw material lot).

The most commonly used indicator of special cause variation is a process with product measurements outside of the **control limits** which are typically set at the process average (X-Bar) plus and minus three standard deviations (SD) of the process variation for the parameter of interest, e.g.; tablet thickness, hardness or thickness.

$$\text{Lower Control Limit} = \text{Process Average} - 3(\text{SD})$$

$$\text{Upper Control limit} = \text{Process Average} + 3(\text{SD})$$

These limits were illustrated and discussed earlier in the “Study Description and Objectives” section of this report (see page 5).

Out-of-Specification (OOS) and **Out-of-Control (OOC)** values require investigation. OOC values are test results that fall outside the process control limits. OOS and OOC values are not always due to manufacturing problems. Such values may also be due to sampling errors, testing errors or human administration errors such as recording errors, data keying mistakes, etc. These causes of OOS and OOC results should be considered when interpreting OOS and OOC results.

When OOC signals are observed it is important to determine the importance of the OOC result. The OOC signal may be an indication of a serious OOC condition that can result in the eventual production of OOS product. Alternatively, the OOC result may be due to random process variation. It is also possible that the OOC signal has prompted the operator to make a process adjustment that has resulted in the process returning to a state of control. In the analysis reported here no critical process shifts were observed. Any OOC signals observed were due to random process variation or resulted in process adjustments which maintained the process in a stable state of operation.

Process Capability Analysis

A **process capability analysis** is conducted to determine the ability of the process to meet the product specifications. The Ppk value is the ratio of the difference between the process average and the nearest specification (minimum of (upper specification – process average, process average – lower specification) divided by 3 times the process standard deviation (SD).

$$\text{Ppk} = \text{Minimum (Upper spec} - \text{Process Avg. and Process Avg.} - \text{Lower Spec}) / 3 (\text{SD})$$

There are two main statistics used to measure capability: 1) percent of the measurements out of specification (OOS) and 2) the process **Ppk value**. The interpretation of the Ppk value is summarized below.

Capability Rating	Ppk Value
Excellent	More than 1.5
Good	1.33 to 1.50
Acceptable	1.00 to 1.33
Poor	Less than 1.0

As the table above shows, any Ppk value greater than 1.0 is considered to be “acceptable” and Ppk indices > 1.5 to be “excellent”. As the Ppk value increases the capability of the process to meet product specifications increases and the performance of the process improves.

A processes with a capability index of Ppk = 2.0 and higher is commonly referred to as a **Robust Process**. When a process is robust small process upsets will not create OOS product. Accordingly, small out-of control signals are not a problem as they do not result in OOS product. A process is said to be “Robust” if its performance is not significantly uninfluenced by variations in process inputs (e.g., raw material lot), process variables (e.g., press force and speed) and environmental variables (e.g., ambient temperature and humidity).

Analysis of Variance

Another important analysis to assess process stability is to study 1) differences between the average performance of two tablet presses, #67 and #71, used to manufacture the tablets and 2) differences between the averages of the Front and Rear chute locations on the tablet presses. This analysis enables the identification of variables that increase variation in tablet parameters and may produce out-of-specification product.

Differences between the presses and the front and rear locations are measured by the differences in average values of product parameters such as weight, hardness and thickness. The relationship between the presses and location is also assessed by studying the interaction between the presses and the tablet chute locations. The ideal situation is that the Press-Location interaction is not statistically significant. A non-significant Press-Location interaction indicates that the differences between the presses are the same at both the Front and Rear tablet chute locations. As a hypothetical but realistic example; assume the following average tablet thickness results were obtained and the statistical analysis (ANOVA discussed below) produced a significant Press-Location interaction.

Press	Front Chute	Rear Chute	Difference
A	2.7	2.6	0.1
B	2.8	2.4	0.4

The interaction is due to the difference between the Front and Rear Chute Average tablet thickness being larger for Press B (Diff = 0.4) than Press A (Diff = 0.1)

The statistical significance of these differences is determined by conducting an **analysis of variance (ANOVA)** technique. The general linear model (GLM) ANOVA was used in many of

the analyses reported in this study. The GLM ANOVA is appropriate because of the different sample sizes in the various data sets.

P-Values: ANOVA produces a p-value for each comparison. A **p-value** is the probability that the observed difference (Press #67 vs. Press #71; Front vs. Rear, Press-Location) is due to random process variation. Adopting standard decision rules, any comparison with a p-value less than 0.05 is considered to be statistically significant.

When evaluating a process for stability, the ideal situation is to find no statistically significant differences. No significant differences in this case mean that there are no important differences between the averages of the presses or the tablet chute locations on the presses. Such a situation is characteristic of a stable process. The decision process is as follows:

1. A null hypothesis (H_0) is assumed; e.g.; there is no difference between the average tablet thickness values for tablets produced by Presses A and B.
2. The alternative hypothesis (H_1) is: the average tablet thickness values are different.
3. A statistical procedure (e.g.; ANOVA) is used to calculate a p-value which is the probability that the difference between the two averages is due to random variation when the null hypothesis is true.
4. Generally accepted practice is used to determine statistical significance. If this probability is larger than 0.10 we conclude that there is no significant difference between the averages and we accept the null hypothesis.
5. If this probability is small, say < 0.05 , we say that it is unlikely that the null hypothesis is true. We thus reject the null hypothesis and conclude that the averages are significantly different (i.e., we accept the alternative hypothesis).
6. The probability range, $0.05 < p < 0.10$, is generally considered a “gray area” in which statistical significance is not as clear and the decision regarding statistical significance is often influenced by subject matter considerations.
7. A useful guideline to remember is that large differences between averages (and other statistics for that matter) are associated with small p-values.

Another important statistic produced as part of the GLM ANOVA is the **adjusted R-Square (R-SQ)** statistic. This statistic measures the percent of variability explained by the model, varying from 0-100%. A low value for this statistic indicates that the variables in the model are not important and are not contributing to the variation observed in the process (a poor predictor of the observed variation). In the analyses reported here, low R-SQ values ($< 30\%$) are an indication of a stable process.

After statistical significance is established the **practical significance** of the difference in average values must be considered. This is frequently done by expressing the observed difference in average values as a percentage of the overall process average. Subject matter expertise is used to evaluate the practical importance of the observed percent difference.

It is helpful to consider the following hypothetical but realistic example. It is assumed that Press A produces tablets from its two chutes with average thickness values of Front = 2.7mm and Rear = 2.6mm; and the p-value for this difference was 0.025. The percent difference would be

$100(0.10)/2.65 = 3.8\%$. Subject matter considerations would need to be considered to determine the practical importance of this difference.

Sample size is an important consideration when determining the importance of a statistically significant difference. It is a mathematical certainty that as the sample size increases the ability to find smaller and smaller differences to be statistically significant increases. When the sample size is large, it is not unusual to find small percentage differences (e.g., <1-2%) to be statistically significant and have no practical significance. Statistical significance by itself is not sufficient to determine the practical importance of a difference. The subject matter and the context of the problem being investigated must also be considered.

Interpreting Practical Significance. As mentioned above subject matter expertise is needed to interpret the practical significance of differences and variable effects. Generally differences less than 5% of the average measurement are considered to be of no practical importance. Of course there are always exceptions to the rule.

Significant differences, due to variables such as tablet press and chute location, can result in increased variation in performance parameters (e.g.; thickness, hardness, weight). The concern is that the wider variation will result in OOS product. This does not appear to be the case here. The Digitek production process was consistently well within the specifications with Ppk values typically > 1.0 (Acceptable) and frequently > 1.5 or 2.0 (Excellent). Such Ppk values are characteristic of a robust process as discussed above. The one exception was in 2006 when two batches had content uniformity outside of specifications.

Nested ANOVA, which is also referred to as one-way or one-variable analysis of variance, is another form of ANOVA used in this study to assess process stability and to estimate the portion of the total variation in the data attributed to various sources of variation. Typically, the larger the percent of the total variation attributed to a source of variation the more important the source of variation. Low amounts (<30%) of Long-Term variation as determined by a nested ANOVA are an indication of a stable process.

Nonparametric Tests Provide a Check on the Conclusions Based on the ANOVA

The ANOVA method makes two assumptions – the unexplained random variation (sampling and measurement variation) in the data: 1) follows a normal distribution and 2) has a homogeneous variance. Nonparametric methods do not make these assumptions and are effective procedures to use to check the results of the parametric statistical procedures, such as ANOVA, when the normality and homogeneous variance assumptions are suspect.

As a check on the conclusions of the ANOVA, two nonparametric procedures were used – **Kruskall-Wallis** test and **Mood's Median** test. Both tests compare the medians (50th percentile) of 2 or more groups of data. As with ANOVA, the p-value is used to determine the statistical significance of the differences observed in the medians. Any p-value less than 0.05 indicates that the associated difference between the medians is statistically significant. Non-significant **Kruskall-Wallis** test and **Mood's Median** tests indicate that the production process is stable.

Homogeneity of Variance

Levene's test was used to compare the variances of the various groups to assess homogeneity of variance within the groups. This procedure does not assume a normal distribution. This test produces a p-value that is used to determine the statistical significance of the differences observed in the variances of the different groups being compared. Any p-value less than 0.05 indicates that the differences between the variances of the different groups are statistically significant. A non-significant **Levene's test** indicates that the variances within the groups are the same. Depending on the use of Levene's test, this indication may be that the assumption of normal distribution is appropriate or that the process is stable, or both.

Normality Tests

Many statistical procedures assume that the data follow normal distribution. **Anderson's test** for normality was used to assess whether the variation within a given group actually follows a normal (Gaussian or Bell-shaped) distribution. This test produces a p-value that is used to determine the statistical significance of the difference between the percentiles of the observed distribution and that of the normal distribution. Any p-value less than 0.05 indicates that the data do not follow a normal distribution. Very small departures from the normal distribution are often found when the sample size is large (e.g., > 100). A non-significant Anderson's test ($p > 0.05$) indicates that the assumption that the data analyzed follow a normal distribution is appropriate.

Trends in Batch Quality 2003 - 2008 Doses 0.125mg and 0.25mg

The purpose of this analysis was to assess the stability of the production process over a long time period using data from the annual product reviews for 0.125mg Dose (2003 – 2008) and 0.25mg Dose (2003 – 2008). The following 10 product parameters analyzed were:

Blend assay (Avg.)	Assay (% of Label)
Blend assay uniformity (RSD)	Content uniformity (Relative standard deviation)
Weight	Weight SD (within-batch variation)
Hardness	Hardness SD (within-batch variation)
Thickness	Thickness SD (within-batch variation)

The approach was to test the statistical significance of the differences of the yearly averages using a one-way ANOVA model. The differences were further checked using the nonparametric Kruskal-Wallis and Mood-Median statistical methods. There were sufficient data available to assess the process capability for Blend assay (Avg), Blend assay uniformity (RSD), Assay (%) and Content uniformity (RSD). The results of this analysis are summarized below in Exhibit A1 for the 0.125mg dose and in Exhibit A2 for the 0.25mg dose.

The Results of the 0.125mg Dose batch trend analysis for 2003-2007 described above supports the conclusion that the manufacturing process was stable of this time period. The only exception is Blend assay and Tablet assay which decreased approximately 2% in the latter part of 2007 but, as noted in the Annual Product Review (APR) "had risen to normal levels for the last 4 batches produced in the year"(Figures 15 and 20).

While there were a few differences found among the yearly averages, all of the differences were very small, less than 1.9% (Tables 1 and 5). The one exception was Content uniformity which showed a 13.8% decrease in 2007, which was a significant improvement, not a problem. It is concluded that the differences among the yearly trends observed are of no practical importance.

The within-year stability of the manufacturing process was assessed by making time plots and control charts of the batch averages and standard deviations. No significant trends were found with the exception of the trends in assay values noted previously.

The capability analysis for the Blend assay, Blend assay uniformity (RSD), Tablet assay and Tablet content uniformity parameters showed that the process was highly capable (Ppk values > 1.2). No out of specification results were found (Table 2A).

The batch trends for 2008 were evaluated by examining the trend graphs and the tabular data presented in the Annual Product Review document for 2008. As shown in Table 2B, no out of specification results were found in 2008 and the annual average statistics and product ranges were comparable to those observed in 2006 and 2007. It is concluded that the 0.125mg Dose production process was stable and capable during 2008.

Exhibit A1 – 0.125mg Dose Batch Trend Analysis 2003 - 2007
Evidence That the Production of Digitek was Stable and Capable
Tables 1,2,5 Figures 1-7, 15-21

Batch Data 2003 - 2007	Analysis	Conclusion
Tables 1 and 5 – Batch Data reported in Annual Product Review – Blend assay, Blend assay uniformity, Tablet weight, hardness, thickness, assay and content uniformity	ANOVA, Kruskal-Wallis and Mood's Median tests	Process is Stable – Differences in annual averages of Tablet weight, hardness and thickness were small (< 1.9%) and of no practical importance.
Tables 2 and 5 – Trend analysis within each year	Time Plot and Control Chart	Process is Stable – No important trends, shifts or cycles were found for Tablet weight, hardness and thickness. Blend assay and Tablet assay were lower in the 2 nd half of 2007, but were well within specifications and returned to normal levels by year end.
Tables 2 and 5 – Blend assay, Blend assay uniformity, Tablet assay (% of label) and content uniformity	Capability	Process is Capable - All Blend assay, Blend uniformity, Tablet assay and content uniformity values were within specification; capability indices (Ppk) were: Blend assay 1.21-5.39; Blend assay uniformity 1.47-2.23; Tablet assay 1.23-2.96; Tablet content uniformity 1.81-4.09. Ppk indices >1.0 are acceptable.

The Results of the 0.25mg Dose batch trend analysis fro 2003-2006 were very similar to those for the 0.125mg Dose. The results summarized below in Exhibit A2 supports the conclusion that the manufacturing process was stable for this time period. The two minor exceptions of note are Blend assay and Tablet content uniformity in 2006. Blend assay decreased slightly in 2006 but returned to normal levels by year end (Figures 27). Tablet content uniformity (RSD) was higher in 2006 due to two outlier batches (Figure 28).

While there were a few differences found among the yearly averages, all of the differences were small varying from 0.3% to 4.3% (Tables 3 and 6). The one exception was Blend uniformity which showed a 20.7% decrease in 2006, which represents a significant improvement, not a problem. It is concluded that the differences among the yearly trends observed are of no practical importance.

Like the analysis for the 0.125mg dose, the within-year stability of the manufacturing process was assessed by making time plots and control charts of the batch averages and standard deviations. No significant trends were found with the exception of the trends in tablet content uniformity RSD values noted previously.

The batch trends for 0.25mg Dose, 2007-2008 were evaluated by examining the trend graphs and the tabular data presented in the Annual Product Review document for 2007 and 2008.

Exhibit A2 – 0.25mg Dose Batch Trend Analysis 2003 - 2006
Evidence That the Production of Digitek was Stable and Capable
Tables 3, 4, 6, Figures 8-14, 22-28

Batch Data 2003 - 2006	Analysis	Conclusion
Tables 3 and 6 – Batch Data reported in Annual Product Review – Blend assay, Blend assay uniformity, Tablet weight, hardness, thickness, assay and content uniformity	ANOVA, Kruskal-Wallis and Mood's Median tests	Process is Stable – Differences in annual averages of Blend assay, Blend assay uniformity, Tablet weight, hardness, thickness and assay were small (0.3%- 4.3%) and of little practical importance. Content uniformity RSD higher in 2006 due to two outlier batches.
Tables 4 and 6 – Trend analysis within each year	Time Plot and Control Chart	Process is Stable – No important trends, shifts or cycles were found for Tablet weight, hardness and thickness. Tablet content uniformity was higher in 2006 due to two outlier batches.
Tables 4 and 6 – Blend assay, Blend assay uniformity, assay (% of label) and content uniformity	Capability	Process is Capable - All Blend assay, Blend uniformity, Tablet assay and content uniformity values were within specification; capability indices (Ppk) were: Blend assay 2.04-2.17; Blend assay uniformity 1.61-2.36; assay 1.65-6.10 content uniformity 0.86-4.20. Two outlier batches produced the 0.86 Ppk value for 2006. Ppk indices >1.0 are acceptable.

As shown in Table 4B, no OOS results were found in 2007 and 2008 and the annual average statistics and product ranges were comparable to those observed in 2006. It is concluded that the 0.25mg Dose production process was stable and capable during 2007 and 2008.

Analysis of the Data on Batch 70924A (Tables 7-12, Figures 29-37)

Conclusions from Data on Batch 70924A

- The API content was uniformly distributed throughout the blend.
- No double-thick tablets were detected by in-process analysis of the tablet weight and thickness data on Batch 70924A. All weight and thickness values were within specifications and no trends were detected. Increased weight and thickness could be associated with double thick tablets but no such trends were detected.

During packaging five double-thick tablets were found. A 100% inspection of entire lot identified another fifteen double-thick tablets. No double-thick tablets have been found outside of the manufacturing facility in any part of the distribution channel including pharmacies and observation by consumers.

- The manufacturing process was stable throughout the production of Batch 70924A. No significant trends, shifts or cycles were detected.
- No out-of-specification results were found indicating that the process is capable of meeting specifications.
- The analysis of the in-process data collected independently by the operators and the QA analysts arrive at the same findings, strengthening the conclusion that the production process is stable and capable. This agreement of results also provides evidence of the integrity of the data collection process.
- Differences in average values of the product parameters (weight, hardness, thickness, assay and content uniformity) due to Press (#67 vs. #71) and Location on press (Front vs. Rear) are very small (<1-2%) and of no practical significance. It is not unusual for very small differences to be statistically significant when the sample size is large as in this case.

These conclusions are based on the analyses summarized in Exhibit B and discussed below.

Blend Uniformity - Production of Batch 70924A

Samples were selected from 10 different locations in the blender. The summary statistics for the 10 samples were: Average = 98.57, Std. Dev. = 1.77 and Relative Standard Deviation (RSD) = 1.80. An RSD = 1.80 is well within the specifications for blend uniformity RSD of 5% indicating that the API content of the blend is uniformly distributed throughout the blend.

QA Start-Up Studies - Production of Batch 70924A (Table 7)

The measurements collected during the start-up phase of the production of Batch 70924A consisted of collecting data on Presses 67 and 71, Front and Rear, at 45 stations. There were 540 measurements taken on the tablet parameters of weight, hardness and thickness.

The analysis, summarized in Table 7, indicated that at start-up the process was both stable and capable. No out-of-specification measurements were found. There were no significant differences among the average values of the 45 samples which represent one rotation of the press. Some small differences between tablet presses (#67 vs. #71) and locations (Front vs. Rear) were detected for weight and hardness. The percent of total variation (R-Square) explained by samples, presses and location was small (Thickness 7.5%, Weight 21.6%, Hardness 27.4%), adding further evidence of a stable process. Adjusted R-Square values < 30% indicate a high degree of process stability.

Exhibit B

Evidence That the Production of Digitek Batch 70924A was Stable and Capable

Data on Batch 70924A	Analysis	Conclusion
Blend assay uniformity	Relative standard deviation (RSD)	Blend assay is uniform - RSD = 1.8% is within the specification of 5%.
Table 7 - QA Start-Up Tablet weight, hardness and thickness	ANOVA	Process is Stable - Stations were homogenous: no differences between tablet presses, small press-location interaction effects; R-Square (R-SQ) low, < 28% depending on tablet parameter indicating a stable process.
	Capability	Process is Capable – All product parameters within specification, capability indices (Ppk) were 1.20, 1.98 and 3.56 for weight, hardness and thickness, respectively.
Table 8 - QA In-Process Sampling, Tablet weight, hardness and thickness	Control Chart	Process is Stable – No trends, shifts or cycles of practical importance were found for tablet weight, hardness and thickness.
	ANOVA	Process is Stable – Differences in press averages and location averages were very small. R-SQ statistics of 1.6%, 0.4% and 3.3% indicating a stable process.
	Capability	Process is Capable - All product parameters within specification, capability indices(Ppk) were 1.39, 1.03, and 2.22; Press 67 was more variable than Press 71 but still capable of meeting specifications.
Table 9 - Operator In-Process Sampling, Tablet weight, hardness and thickness	Control Chart	Process is Stable – No trends, shifts or cycles of practical significance were found for Tablet weight, hardness and thickness.

Exhibit B (cont'd) Data on Batch 70924A	Analysis	Conclusion
Table 9 - Operator In-Process Sampling, Tablet weight, hardness and thickness	ANOVA	Process is Stable – Differences in press averages and location averages very small. R-SQ statistics all less than 0.9% indicating a stable process.
	Capability	Process is Capable - All Tablet weight and thickness measurements were within specification, capability indices (Ppk) were 1.15, 1.13 and 2.56; Press 67 was more variable than Press 71 but still capable of meeting specifications.
Table 10 – Operator and QA Sampling Data Combined; Tablet weight, hardness and thickness	Control Chart	Process is Stable – No trends, shifts or cycles of practical significance were found for Tablet weight, hardness and thickness.
	ANOVA	Process is Stable – Differences in press averages and location averages very small. R-SQ statistics all less than 3.6% indicating a stable process.
	Capability	Process is Capable - All Tablet weight, hardness and thickness measurements within specification, capability indices (Ppk) were 1.11, 1.08 and 2.43; Press 67 was more variable than Press 71 but still capable of meeting specifications.
Table 11 – Operator and QA In-Process Sampling data - Tablet weight, hardness and thickness	ANOVA – Separate for each of the 4 Data Source – Press combinations	Process is Stable – Percent long-term variation (indicator of process stability) varied from 3-38% indicating a stable process. Percent long-term variation is only a concern for stability when it is > 30%.
Table 12 – Tablet content uniformity – Actavis and 484 Sampling Data	Levene's Test for Homogeneity of Variance	Tablet Content is Uniform – All Relative standard deviation (RSD) values are within the 6% specification. 0.125mg Dose RSD values were both homogeneous within and between data sources (Actavis and 484 Sampling). 0.25mg Dose RSD values somewhat higher but within specification.

QA Start-Up Studies - Production of Batch 70924A (Table 7)

Measurements for Batch 70924A consisted of collecting data on Presses 67 and 71, Front and Rear, at 45 stations during the start-up phase of production. There were 540 measurements taken on the tablet parameters of weight, hardness and thickness.

The analysis, summarized in Table 7, indicated that at start-up the process was both stable and capable. No out-of-specification measurements were found. There were no significant differences among the average values of the 45 samples which represent one rotation of the press. Some small differences between tablet presses (#67 vs. #71) and locations (Front vs.

Rear) were detected for weight and hardness. The percent of total variation (R-Square) explained by samples, presses and location was small (Thickness 7.5%, Weight 21.6%, Hardness 27.4%), adding further evidence of a stable process. Adjusted R-Square values < 30% indicate a high degree of process stability.

QA In-Process Sampling - Production of Batch 70924A (Table 8, Figures 29-31)

The goal of the analysis of the QA In-Process data was to determine if there were any sources of variation present that could contribute to a lack of process capability of meeting specifications and process stability. As shown in the following paragraphs of this section, the QA In-Process data showed the manufacturing process to be stable producing product that met specifications with no out-of specification results found.

The capability analysis (with data from both presses combined) found: 1) no out-of specification values and 2) process capability statistics that were “acceptable to excellent” with Ppk values of 1.39, 1.03 and 2.33 for Weight, Hardness and Thickness, respectively.

The data were subjected to a control chart analysis to check for process stability. The tablet weight, hardness and thickness values were found to be stable and in a state of statistical control.

The state of process stability was confirmed when a variance components analysis (Table 11) was done separately for each press. It was found that the amount of variation associated with process stability (Long-Term variation) was: 2.4%, 31.9%, 20.7%, 7.9%, 18.3% and 18.2% depending on Press and tablet parameter; weight, hardness and thickness. As noted earlier, the lower the long-term variation on a percentage basis, the more stable the process. Any Long-Term variation <30% is acceptable and an indication of a stable process.

Next, differences in the average performance (tablet weight, hardness and thickness) between the tablet presses (#67 vs. #71) and locations (Front vs. Rear) were compared using a general linear analysis of variance (ANOVA) model. Differences between the presses, locations and the Press-Location interaction were tested. Small differences in the averages were found for presses (average weight difference <0.4%; average hardness difference <0.6%). These differences are small and do not have any practical significance. The finding of stability discussed above was further supported by this analysis which had Adjusted R-Squared values ranging from 0.4% to 3.3%. Adjusted R-Square is a measure of long-term variation; low R-square indicates higher process stability.

Levene's test for homogeneity of variance showed that Press 67 was more variable than Press 71 for hardness and thickness but still capable of meeting specifications for these parameters.

Process Operator In-Process Sampling - Batch 70924A (Table 9, Figures 32-34)

The goal of the analysis of the Operator In-Process data was to determine if there were any sources of special cause variation present that could contribute to lack of process capability of meeting specifications and process stability. As discussed below, the Operator In-Process data

showed that the manufacturing process was stable producing product that met specifications with no out-of specification (OOS) results found for weight, hardness and thickness.

The capability analysis (with data from both presses combined) showed process capability statistics that were “acceptable to excellent” with Ppk values of 1.13, 1.15 and 2.65 for tablet weight, hardness and thickness, respectively. As noted above, no out-of specification results found for weight, hardness and thickness.

The data were subjected to a control chart analysis to check for process stability. The tablet weight, hardness and thickness values were found to be stable and in a state of statistical control. The state of process stability was confirmed when a variance components analysis was done separately for each press (Table 11). It was found that the amount of variation associated with process stability (long-term variation) was 13.2%, 19.2%, 3.4%, 37.9%, 23.4% and 32.0%; depending on which tablet press (#67, #71) and which tablet parameter (weight, hardness and thickness) was analyzed. As noted earlier, the lower the long-term variation on a percentage basis, the more stable the process. Any Long-Term variation <30% is acceptable and an indication of a stable process.

Next, differences in the average performance (tablet weight, hardness and thickness) between the tablet presses (#67 vs. #71) and locations (Front vs. Rear) were compared. Small differences were found between the presses. Press 67 produced hardness values that were 0.028% higher than Press #71. This effect was so small as to not have any practical significance. The analysis was made using a general linear analysis of variance (ANOVA) model testing differences between the presses, locations and the Press-Location interaction. The finding of stability discussed above was further supported by this analysis which had Adjusted R-Squared values ranging from 0.4% to 0.8%.

As found in the analysis of the QA data, Levene’s test for homogeneity of variance showed that Press 67 was more variable than Press 71 for hardness and thickness but still capable of meeting specifications for these parameters.

QA and Operator In-Process Data - Batch 70924A (Tables 10-11, Figures 35-37)

The QA In-Process and Operator In-Process data sets monitor the same process. The operators sampled the process every 30 minutes. QA sampled the process every hour. It is useful to combine the QA and Operator data sets. The sample size is increased, thereby increasing the ability of the analysis to detect trends and differences. The analysis of the combined data sets used the same methodology as that described above when the two sources of data were analyzed separately.

The goal of this combined analysis was to see if there were any sources of special cause variation present that could contribute to a lack of process capability of meeting specifications and process stability. As shown below, the combined QA In-Process and Operator In-Process data showed that the manufacturing process was stable producing product that met specifications with no out-of specification results found for weight, hardness and thickness.

The capability analysis of the combined data sets produced process capability statistics that were “acceptable to excellent” with Ppk values of 1.08, 1.11 and 2.43 for tablet weight, hardness and thickness, respectively. As mentioned above, no out-of specification results found for weight, hardness and thickness.

The data were subjected to a control chart analysis to check for process stability. The tablet weight, hardness and thickness values were found to be stable and in statistical control.

Next differences in average performance (Tablet weight, hardness, thickness) between the tablet presses (#67 vs. #71) and locations (Front vs. Rear) were compared using a general linear analysis of variance (ANOVA) model. This analysis enabled the testing for differences between the presses, locations and the Press-Location interaction. Small differences in the average performance were found between presses (average weight difference <0.4%; average hardness difference <0.6%). However, these effects were so small as to not have any practical significance. The finding of stability discussed above was further supported by this analysis which had Adjusted R-Squared values ranging from 0.5% to 3.5%.

Content Uniformity - Production of Batch 70924A and 484 Sampling (Table 12)

There were two sources of Tablet content uniformity data collected on Batch 70924A: 1) Samples collected by Actavis (4 samples from Batch 70924A) and 2) 484 Sampling done by the FDA (4 samples from various batches) for 0.125mg Dose. The tablet content uniformity relative standard deviations were compared using Levene’s test for equality of variances. The Actavis and 484 Sampling RSD values were compared using a one-variable ANOVA.

The eight relative standard deviation (RSD) values for the 0.125mg dose varied from 0.8 to 2.1%, all being within the 6% specification. The RSD values are related to the within-sample variation. The within-sample variances were compared to determine if the variation within the different samples were the same for all the samples. The results of the analysis are summarized below:

Study of Within-Sample Equality of Variance and Conclusions

Comparison	Conclusion
All RSD values are within specification of 6% with a range of 0.8-2.1	Tablet content uniformity meets specifications
All 8 samples – Within-sample variance (p=0.516)	Samples do not have a significantly different tablet content uniformity
Actavis Data - 4 Samples – Within-sample variance (p=0.091)	Samples do not have a significantly different tablet content uniformity
484 Sampling Data - 4 samples – Within-sample variance (p=0.829)	Samples do not have a significantly different tablet content uniformity
Actavis vs. 484 Sampling – Within-sample variance (p=0.614)	Samples do not have a significantly different tablet content uniformity

The p-values for these comparisons are all greater than 0.05 indicating that none of the RSD values compared were significantly different. The finding that all RSD values were within

specification and the comparisons summarized above supports the conclusion that the API content of the tablets in the batch was uniform.

Analysis of Stability Data (Tables 13-14)

The product data analyzed consisted of assay and dissolution stability test data collected by third party labs (Defendant's Exhibits 83 and 84). A total of 33 tests were reported but only 29 tests had data to analyze for stability trends (18 tests for 0.125mg Dose and 11 tests for 0.25mg Dose). Data were reported for 0, 3, 6, 9, 12, 18, 24 and 36 months on test. The product expiration was 18 months. As discussed below the product was found to be stable at both dose levels for both assay and dissolution. The following conclusions were reached:

0.125mg Dose is stable with respect to Assay and Dissolution

- No significant differences were found among the monthly means (GLM ANOVA: Assay $p=0.521$; Dissolution $p=0.336$).
- The linear trend over months was not statistically significant (GLM ANOVA; Assay $p=0.221$, Dissolution $p=0.820$).

0.25mg Dose is stable with respect to Assay and Dissolution

- No significant differences were found among the monthly means (GLM ANOVA; Assay $p=0.632$; Dissolution $p=0.362$).
- The linear trend over months was not statistically significant (GLM ANOVA: - Assay $p=0.141$; Dissolution $p=0.198$).

The conclusions that Digitek is stable over the 18 month time period at both dose levels are based on subjecting the stability data (Tablet assay and dissolution) to a General Linear Model Analysis of Variance (GLM ANOVA). The analyses were done separately for Doses 0.125mg and 0.25mg and separately for Tablet assay and dissolution producing a total of four separate analyses.

This analysis included effects for "Month" and "Test". The averages for the months (0, 3, 6, 9, 12, 18, 24, 36) were compared to determine if the product was stable over time. Effects for the different tests (18 tests for 0.125mg Dose and 11 tests for 0.25mg Dose) were included in the model to account for any variation introduced by the different tests. In a second analysis, the linear effect for time on test (month) was tested also using the GLM ANOVA model including a model term for the different tests.

Celsis tested three batches (60992A, 61097A and 61100A) for tablet assay (% of label), content uniformity and dissolution. The following results

Variable	Batch	N	Mean	StDev	RSD	Minimum	Maximum
Content Uniformity	60992A	10	98.670	1.334	1.35	96.900	101.000
	61097A	10	101.02	1.27	1.26	98.60	102.90
	61100A	10	99.200	0.826	0.83	97.700	100.600
Dissolution	60992A	6	100.80	1.61	1.60	99.20	102.40
	61097A	6	99.683	1.577	1.58	97.300	101.800
	61100A	6	99.48	2.66	2.67	96.60	102.70

indicate that the Content uniformity (RSD) and Dissolution parameters were within specification (RSD < 6%, Dissolution >80%). The Tablet assay values for the three batches were: 99.4, 97.5 and 99.4%, respectively, all being well within the specifications of 90-105%.

Analysis of Batches 70836A, 70925A, 70207A, 70770A and 80228A

Batch 70836A (0.25mg Dose) was of particular interest as it was manufactured immediately prior to the manufacture of Batch 70924A using Tablet Presses 67 and 71 which were the same two tablet presses used to manufacture Batch 70924A. The analysis showed that the manufacturing process was both stable and capable with no problems observed (Tables 15-16).

- The blend assay and blend uniformity values were within specifications for blend assay = 97.8% (specification 90-110) and blend uniformity RSD = 2.6 (specification = 5%).
- The tablet content uniformity had RSD = 1.7% which is well within the 6% specification.
- No out-of-specification tablets were found for weight, hardness and thickness by either the operators or QA sampling.
- The control chart analysis showed the process was stable for the tablet, weight, hardness and thickness parameters.
- Operator in-Process sampling data produced process capability Ppk indices of 1.29, 2.31 and 6.18 for tablet weight, hardness and thickness parameters, respectively.
- The Operator and QA Sampling data were in agreement regarding the stability and capability of the tablet weight, hardness and thickness parameters.

Batch 70925A (0.125mg Dose) was also of particular interest as it was manufactured immediately after Batch using Tablet Presses 70 and 71. The analysis showed that the manufacturing process was both stable and capable with no problems observed (see Tables 17-18).

- The blend assay and blend uniformity values were within specifications for blend assay = 99.3% (specification 90-110) and blend uniformity RSD = 2.2 (specification = 5%).
- The tablet content uniformity had a RSD = 1.4% which is well within the 6% specification.
- No out-of-specification tablets were found for weight, hardness and thickness by either the operators or QA sampling.
- The control chart analysis showed the process was stable for the tablet, weight, hardness and thickness parameters.
- Operator in-process sampling produced process capability Ppk indices of 1.31, 1.76 and 4.80 for tablet weight, hardness and thickness parameters, respectively.
- The Operator and QA Sampling data were in agreement regarding the stability and capability of the tablet weight, hardness and thickness parameters.

There was a concern regarding blend uniformity of **Batch 70207A** when one low blend value of 87.3% was obtained. The remaining 9 sample values were within specification. Another set of 10 samples were taken and analyzed; all 10 samples were within specification. After the tablets were compressed, 4 samples of 10 tablets were analyzed for content uniformity. The resulting

acceptance values of 9.31, 4.21, 2.40 and 3.61 were all well within the 15% specification for acceptance value. These data indicate that Batch 70207 did not have any blend or tablet content uniformity issues.

Blend uniformity was also a concern for **Batch 70770A**. A low value of 67.9% was observed for one of the samples in the first set of 10. The low value was confirmed on reanalysis. Two additional sets of 10 samples were collected and analyzed. All 20 samples were within specifications.

To determine if the measurement system was at fault, an Analysis of Variance of the 29 values was conducted. The one atypically low value of 67.9 was omitted from this analysis because it was due to sampling variation not measurement variation which was the subject of this analysis. The ANOVA of the three sample sets showed that there were no significant differences between the average values of the sample sets. This provides further evidence that the one atypical result was an isolated event and not due to systematic measurement problems. The tablet content uniformity sample and analysis produced an acceptance value of 4.7% which is well within the 15% specification. These results indicate that Batch 70770A did not have any blend or tablet content uniformity issues.

Batch 80228A was rejected because of overweight filled bottles identified during the packaging operation. The OOS bottles were traced to some out-of-specification (OOS) tablets. No OOS tablets were detected by routine operator and QA sampling during production. The subject batch was produced using Tablet Press 81.

Analysis of the tablet weight data collected by the Operators and QA was conducted to assess process capability and stability during the manufacture of this batch. As the following results indicate these data did not detect any process and capability problems:

- The control chart analysis showed the process to be “in-control”. Three outlier samples beyond the control limits had no effect on the stability conclusion.
- No out-of-specification tablets were found.
- The process capability index of $Ppk = 1.86$ was in the “Excellent” category.
- There was no significant difference between the average thickness values associated with the Front and Rear chutes.
- The long-term variation was approximately 30% of the total variation indicating that the process was stable.

It is concluded that the OOS bottles and associated tablets were due to an isolated event and not due to any systematic or chronic production problems.

Comparison of Production and Validation Batches (Figures 38-43)

An important question to ask is:

“Are Batches 70836A, 70924A and 70925A significantly different from the validation batches manufactured in 1994 and 1996? Has the manufacturing process changed since it was validated?”

Three **validation batches for 0.125mg Dose** were manufactured in 1994 (Batches 4318A, 4320A, 4322A) and two validation batches were manufactured in 1996 (Batches 6221A, 6250A). The analysis was conducted by comparing the five validation batches with two production batches, Batch 70924A (source of a few double thick tablets) and Batch 70925A which was manufactured immediately after Batch 70924A.

As shown in Figures 38-40 there are no significant difference between the validation batches and the two production batches. The results of these two production batches (tablet weight, hardness and thickness) were very consistent with those obtained on the validation batches in 1994 and 1996.

In 1995 a study was done at 28 revolutions-per-minute (rpm) to more accurately define the upper press speed limit for the 0.125mg dose. Three batches (5068A, 5069A, 5070A) were run. Tablets were sampled and tested after 1 and 5 minutes. All results (Tablet weight, thickness, hardness) were within acceptable limits and consistent with the validation batches run in 1994 and 1996. It was concluded that the allowable press speed range for the 0.125mg dose would be 14 – 28 rpm with a normal speed of 21 rpm

Three **validation batches for 0.25mg Dose** were manufactured in 1994 (Batches 4330A, 4336A, 4337A). The analysis was conducted by comparing the three validation batches with the production batch 70836A.

As shown in Figures 41-43 there are no significant difference between the validation batches and the production batch. The results of production batch 70836A (tablet weight, hardness and thickness) were very consistent with those obtained on the validation batches in 1994.

Comparison of Batches 70836A, 70924A and 70925A (Tables 15-20)

Another important study is the comparison of Batches 70836A, 70924A and 70925A. Batches 70836A and 70925A were manufactured immediately before and after Batch 70924A, respectively. As discussed previously, the analysis concluded that the manufacturing process was stable and capable during the manufacture of Batch 70924A. Was this high level of manufacturing capability present during the time period in question? The analysis reported in the following paragraphs concludes that the manufacturing process was stable and capable during the manufacture immediately before and after Batch 70924A as well as during the manufacture of Batch 70924A.

In Tables 15-18 we see that the manufacturing process was both stable and capable during the production of both lots 70836A and 70925A. No out-of-specification product was observed and the process capability index Ppk was “acceptable to excellent” for tablet weight, hardness and thickness in both batches. The Ppk values ranged from approximately 1.0 to more than 6.0 depending on the product parameter. As has been observed for other batches, the trends observed for both the QA Sampling and the Operator sample were very consistent across the data sets.

Batch	Sample	Weight Ppk	Hardness Ppk	Thickness Ppk
70836A	QA	0.97	2.34	5.17
70836A	Operator	1.29	2.31	6.18
70925A	QA	1.91	1.78	2.91
70925A	Operator	1.31	1.96	4.8

Some differences in the average values of the tablet presses and locations on the presses (Front vs. Rear) were observed. But as was determined for other batches, these differences were very small, varying from approximately 0.2% to 4.6%, which are of little practical significance.

Comparisons of the process and capability statistics for the three batches, 70836A, 70924A and 70925A, are summarized in Tables 19-20. The statistics for the three batches are in very good agreement, indicating that the process was stable and capable during the production of these three batches. It is concluded that the process was stable and capable before, during and after the production of Batch 70924A.

Summary of Analyses

The pharmaceutical in question, Digitek, Doses 0.125mg and 0.25mg, was made according to a specified formulation and a defined manufacturing process. Many checks were in place to ensure that Digitek was manufactured according to the prescribed formulation and manufacturing process. These checks produced no significant deviations.

Another check on the quality of the manufacturing process is to conduct a statistical evaluation of the data collected during the operation of the process. The analysis focused on two sources of production data: 1) data collected on the different batches produced from 2003-2008 for Doses 0.125mg and 0.25mg as reported in the Annual Product Review documents and 2) data collected during the production of Batch 70924A. These data were used to assess the stability and capability of the manufacturing process during the production of Batch 70924A and over the 2003-2008 time period. Data collected by third parties including Celsis and other independent labs, FDA and Quantic were also analyzed.

Batch Trends Analysis 2003 – 2007 Doses 0.125mg and 0.25mg

The analysis of the batch trends for the 0.125mg and 0.25mg Doses were in agreement that the Digitek production process was stable and capable during the time the data were collected. This is very strong evidence, covering 5 years of production involving approximately 500 batches of product, that the process was consistently producing product that met specification..

Batch 70924A Production Data

A variety of statistical analyses were applied to the Batch 70924A production data. In all cases the processes were found to be stable and capable. Small differences being typically < 1-2 %, were found due to tablet presses and yearly variation. It is not unusual for such differences to be

found given the large sample sizes of the available data sets. It is very unlikely that these small differences have any practical significance.

No double-thick tablets were detected by this analysis of the tablet weight and thickness data on Batch 70924A. All weight and thickness values were within specifications. Increased weight and thickness could be associated with double thick tablets but no such trends were detected.

Evaluation of Batches 70836A and 70925A Produced Before and After Batch 70924A

Analysis of the test data for Batches 70836A and 70925A, which were manufactured immediately before and after Batch 70924A respectively, indicated that this batch was well within specifications, No OOS results were found; the blend assay and content uniformity results were within specifications. It is concluded that production process was stable and capable during the manufacture of these batches, providing additional evidence of the credible performance of the manufacturing process.

A comparison was made of the process capability statistics for Batch 70924A with the same statistics of Batches 70836A and 70925A were manufactured immediately before and after Batch 70924A. The analysis showed that the stability and capability statistics for the three batches are in very good agreement. This indicates that the process was stable and capable during the production of these three batches. This finding leads us to the conclusion that the production process was stable and capable before, during and after the production of Batch 70924A.

Comparison of Batches 70836A, 70924A and 70925A with Validation Batches

0.125mg Dose. A comparison of in-process data collected by the process operators for Batches 70924A and 70925A was made to similar data from five validation batches (0.125mg dose) manufactured in 1994 and 1996. It is concluded that there are no significant differences between the validation batches and the two production batches indicating that the process that produced these two batches had the same performance as the process that was validated in 1994 and 1996.

0.25mg Dose. A comparison of production test data for Batch 70836A was made to similar data from three validation batches (0.25mg dose) manufactured in 1994. It is concluded that there are no significant differences between the validation batches and the production batch indicating that the process that produced Batch 70836A had the same performance as the process that was validated in 1994.

The validation data were not compared to the data collected by QA for batches 70836A, 70924A and 70925A as the QA data were shown earlier to be essentially the same as the in-process data collected by the process operators. There was only one set of validation results for each batch. The production batches were sampled by both QA and the process operators.

Analysis of Batches 70207A, 70770A and 80228A

Analysis of the Batch 70207A and 70770A test data showed blend uniformity was not an issue for these batches. In both cases, the single atypical values were not confirmed by resample. All of the resample blend uniformity acceptance values were within the acceptance value of 15%.

Analysis of the tablet weight data for Batch 80822A showed there were no significant trends in the tablet weight data. It is concluded that the OOS bottles and associated tablets were due to an isolated event and not due to any systematic or chronic production problems.

Third Party Testing and Reviews

Several third party tests and reviews were made of the Digitek production process.

- An evaluation of information from 25% (38/152) of the 152 recalled batches was made by Quantic and Third Party Labs and no problems were found. This evaluation consisted of review of batch records by Quantic and testing of product by Third Party Labs.
- Third party labs tested eight batches for product stability in 33 separate tests for 0.125mg and 0.25mg doses and found no product stability problems.
- FDA 484 Sampling of 11 batches found no content uniformity problems for 0.125mg and 0.25mg doses.

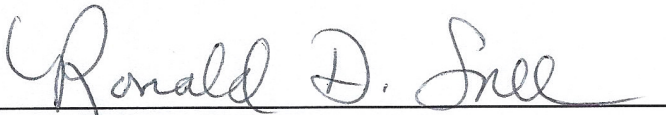
None of these studies identified any production problems. The content uniformity data analysis found that all tablet content uniformity RSD values were within specification. The RSD values were homogeneous within Actavis samples and FDA 484 Sampling data. There was no significant difference between the RSD values of the Actavis and 484 Samples. This leads to the conclusion that the API content of the tablets in the batches sampled was uniform.


Analysis of the third party testing stability data showed that the 0.125mg and 0.25mg doses were stable for assay and dissolution (only parameters tested) over the 36 month time period.

Celsis also tested three batches for tablet assay (% of label), content uniformity and dissolution. The tests showed that all three tablet parameters were within specification.

Conclusion

It is concluded that the Digitek manufacturing process was stable and capable over the 2003 – 2008 time period and particularly during the production of Batch 70924A. No systematic or chronic manufacturing problems were identified. These findings together with the finding of no out-of-specification product during the production of Batch 70924A indicate that the process was consistently producing product that met specifications.


Ronald D. Snee, PhD


Date

References for Statistical Methods Used

Conover, W. J. (1999) Practical Nonparametric Statistics, 3rd Edition, John Wiley and Sons, New York, NY

Montgomery, D. C. (2009) Introduction to Statistical Quality Control, 6th Edition, John Wiley and Sons, New York, NY

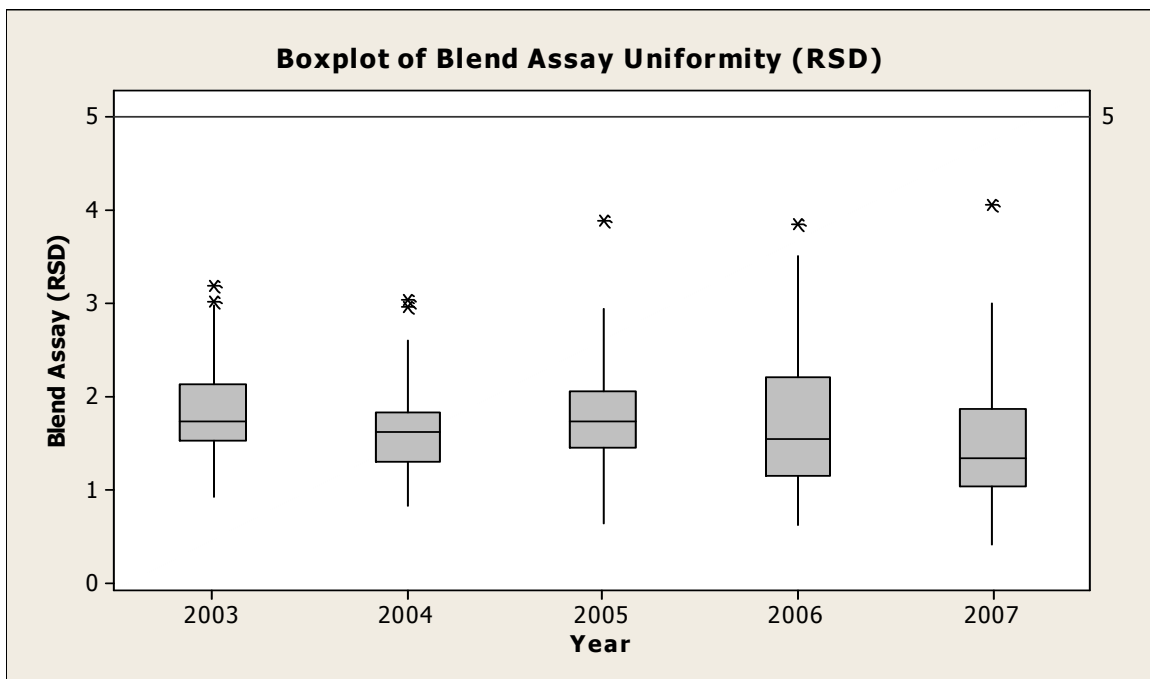
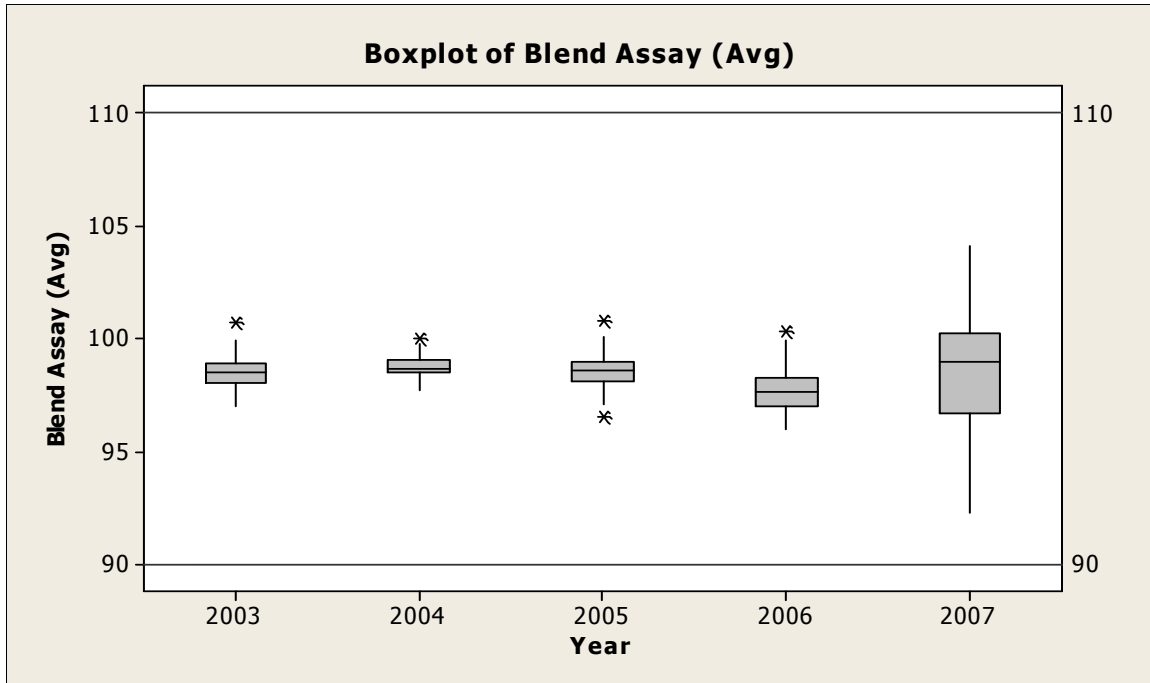
Documents Reviewed

- Annual Product Reviews for 2003 – 2008, Doses 0.125mg and 0.25mg
- Batch Record Data for Batch 70924A
- FDA 484 Sampling Reports
- Process Validation Report for 0.125mg Dose prepared on December 23, 1994
- Process Validation Report for 0.125mg Dose prepared on September 11, 1996
- Process Validation Report for 0.25mg Dose prepared on December 29, 1994
- 483 Letters
- Celsis Stability Test results on Behalf of UDL - Defendant's Exhibits 83 and 84
- Celsis testing of Batches 60992A, 61097A and 6110A
- Batch Records for Batches 70207A, 70770A, 70836A, 70925A and 80228

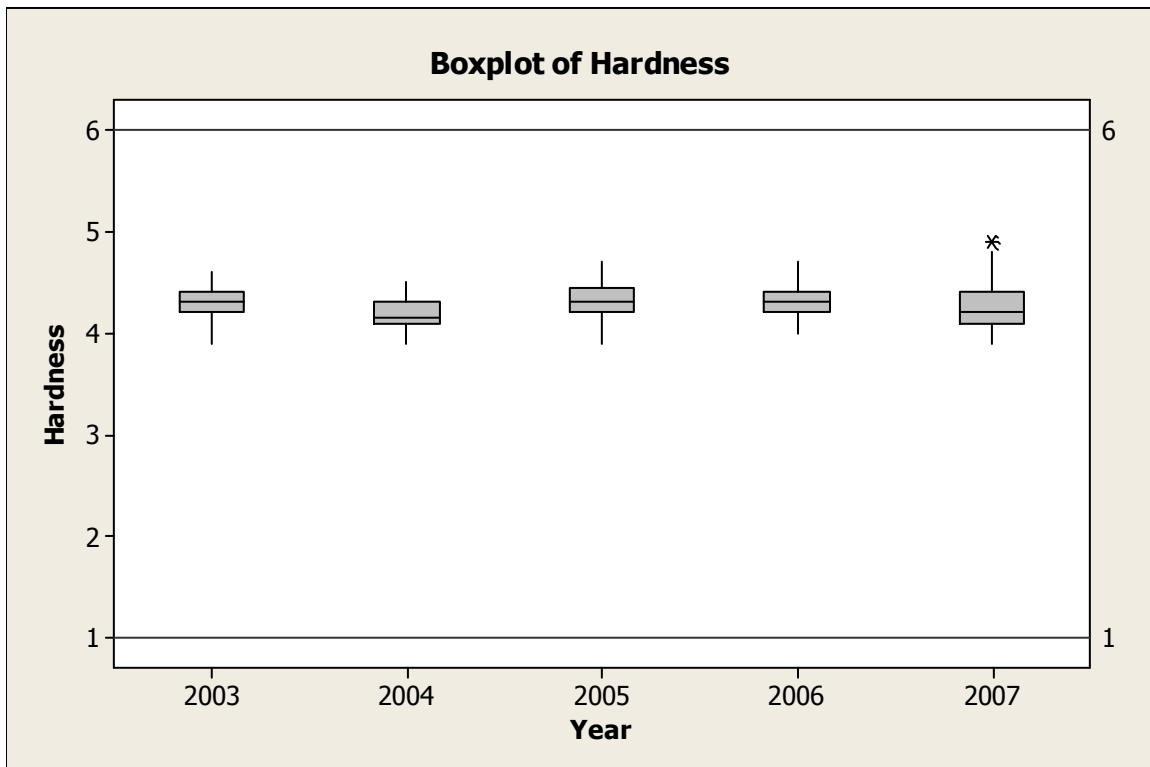
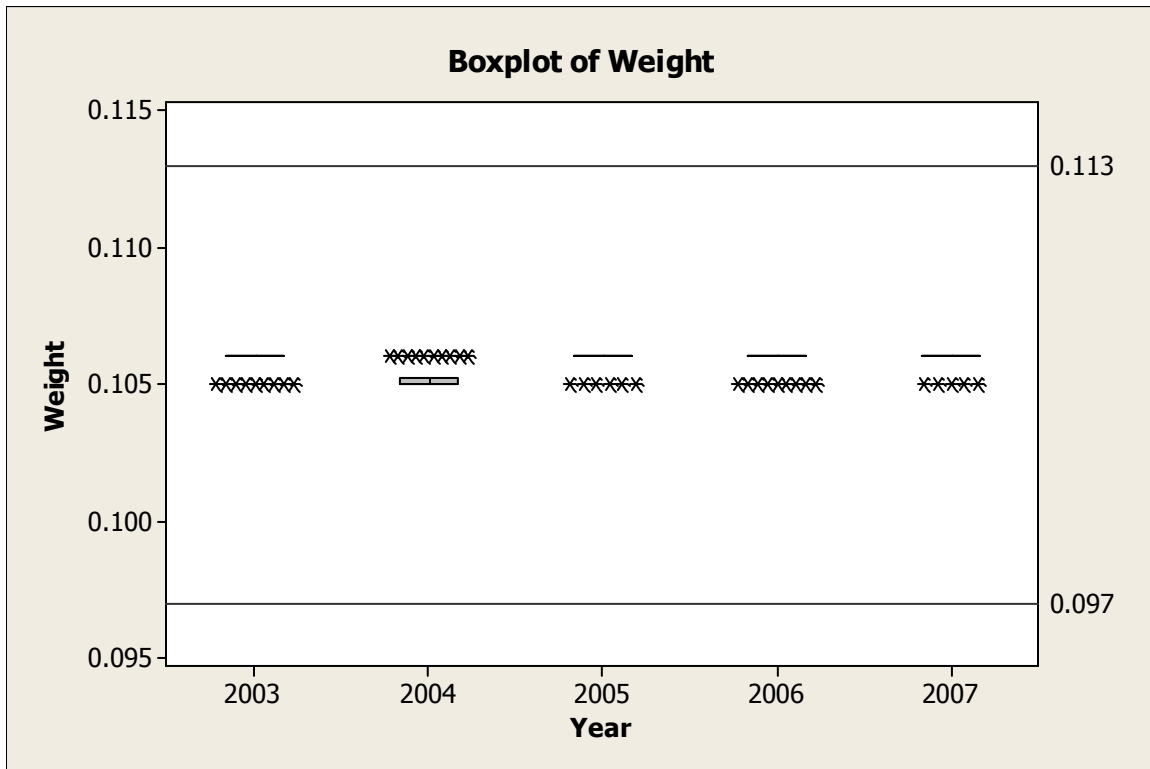
Figures 1- 7 0.125mg Dose
Boxplots of Batch Variation Within and Between Years 2003 – 2007

The Boxplot Shows the Median Value of the Data, the Central 50% of the Distribution Denoted by the “Box” and the Extremes of the Data

Figures 1-2. Blend Assay and Blend Assay Uniformity (RSD)



Figures 3-4. Batch Average Tablet Weight and Hardness



Figures 5-6. Batch Average Tablet Thickness and Assay (% of Label)

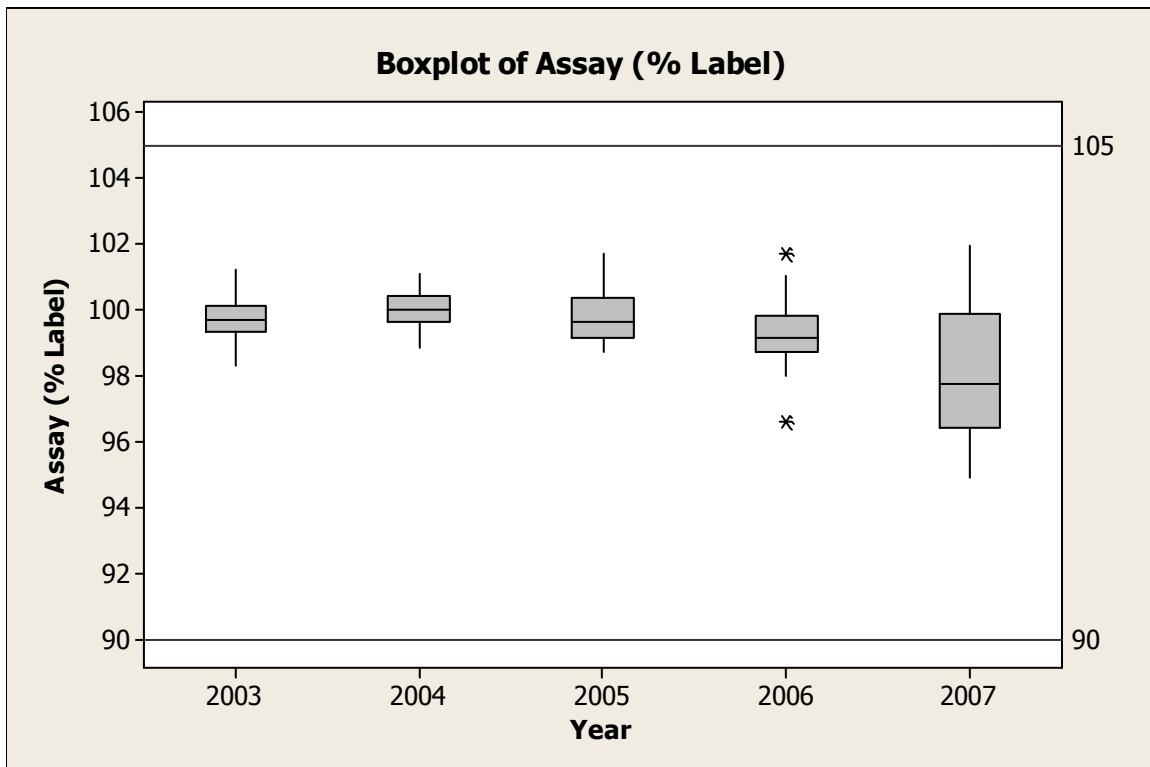
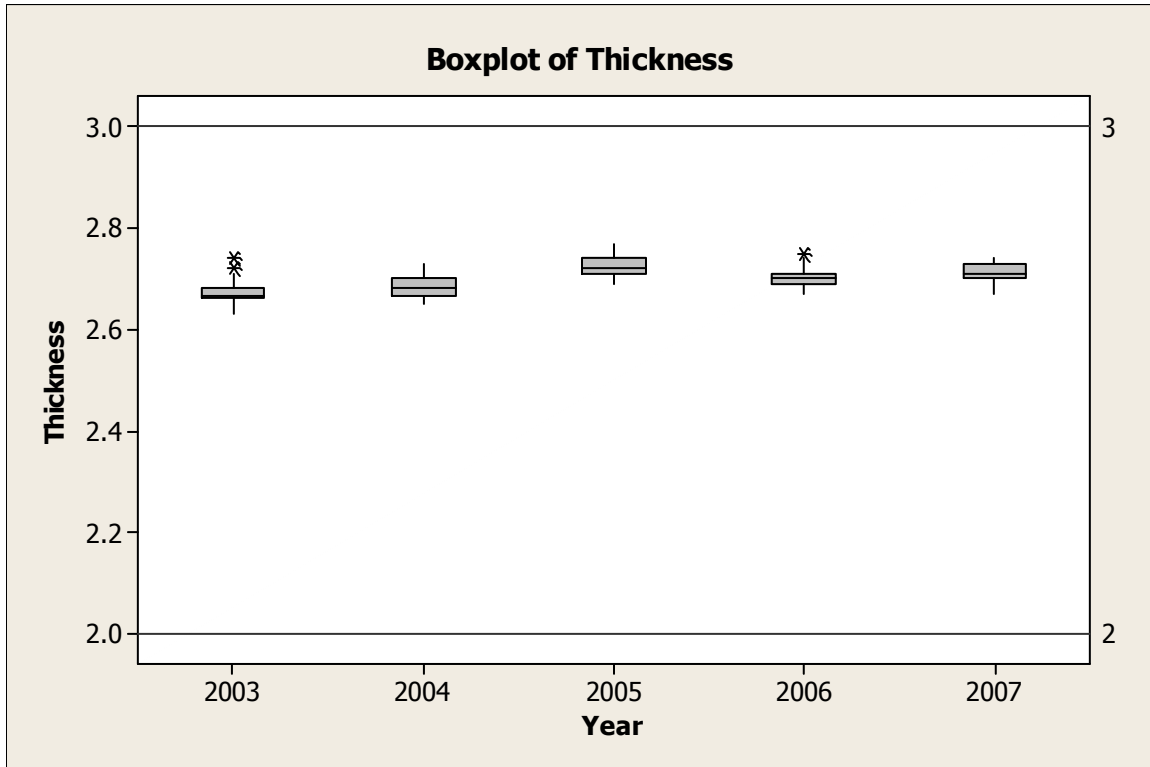
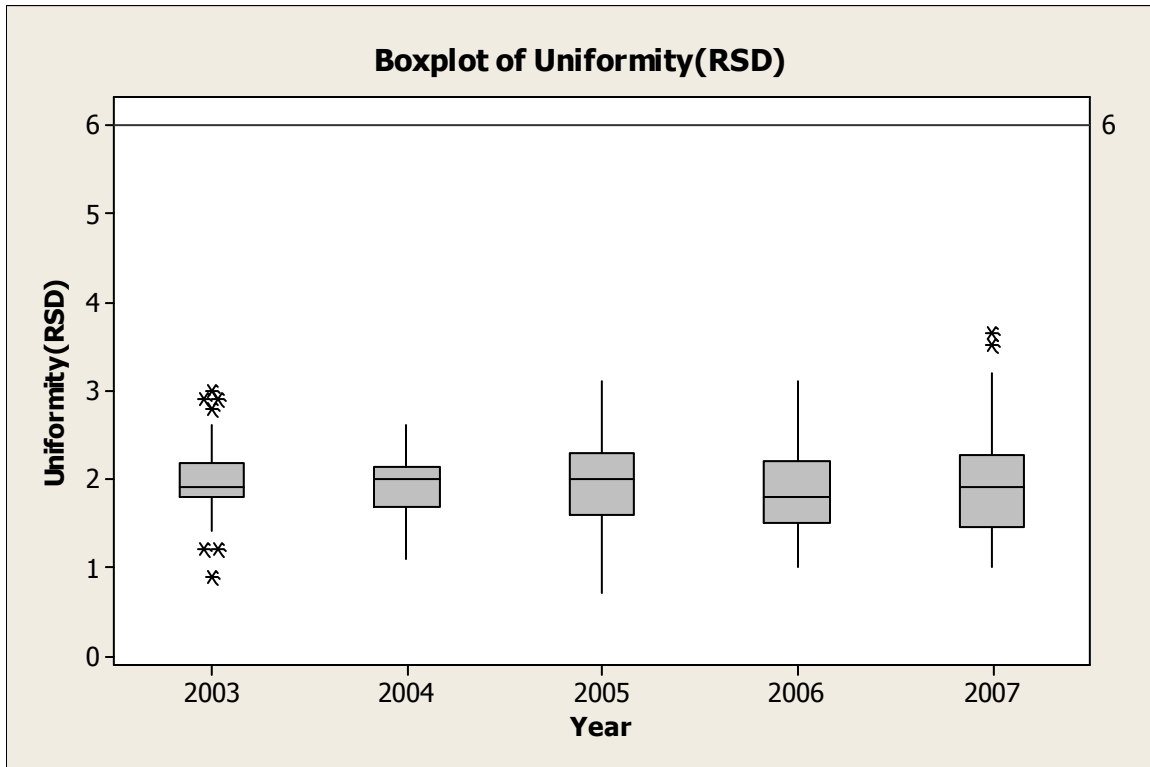
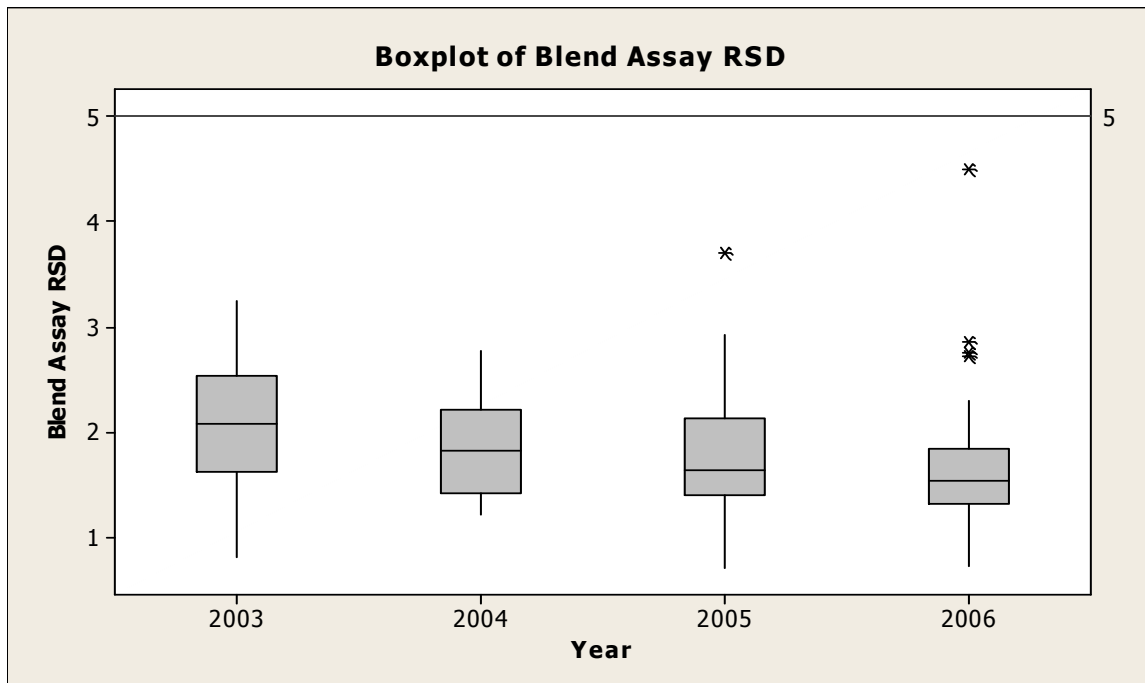
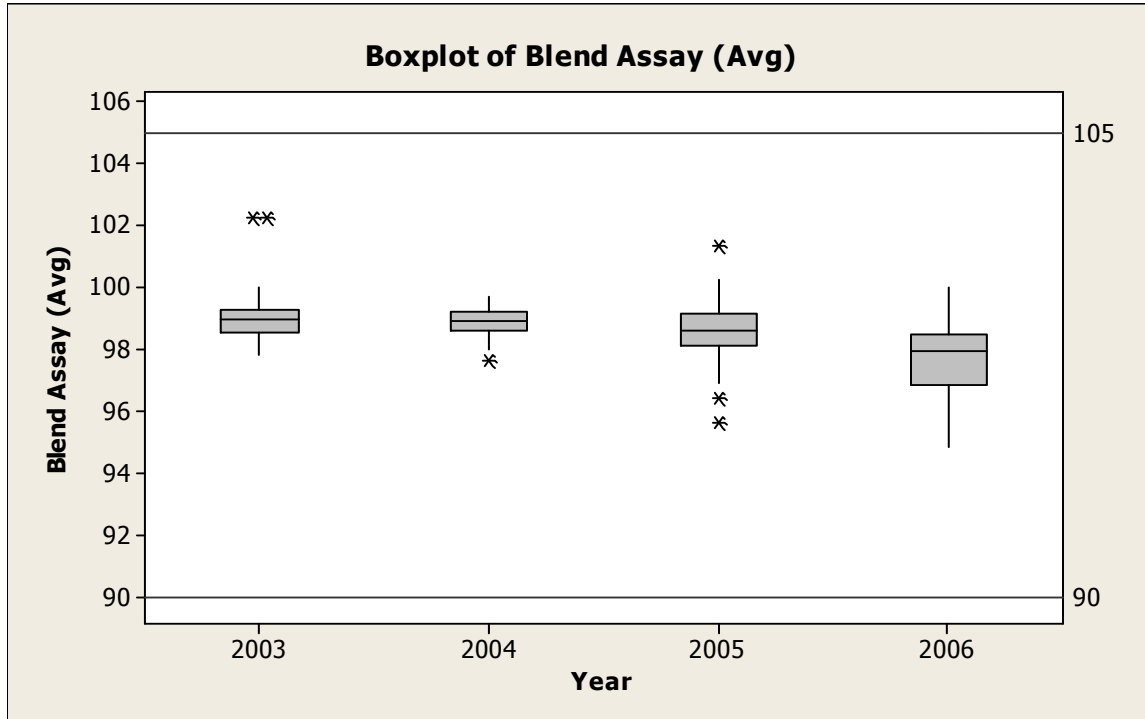


Figure 7. Batch Average Tablet Content Uniformity (RSD)

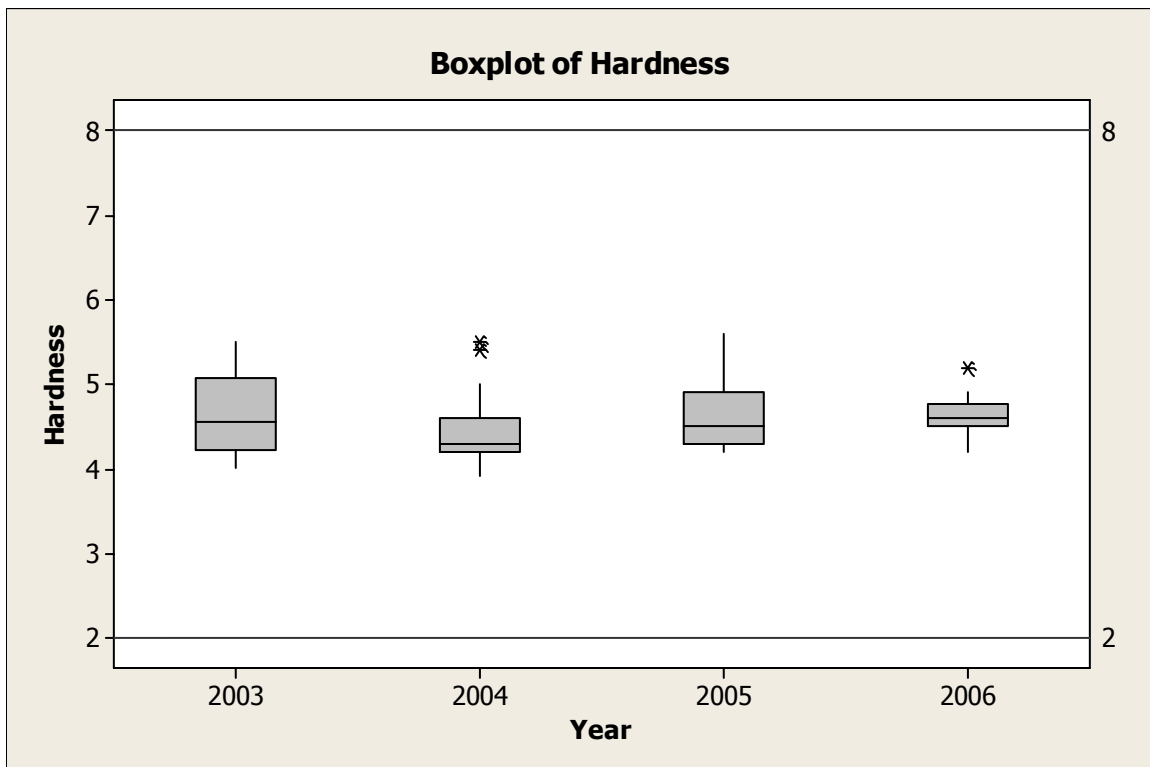
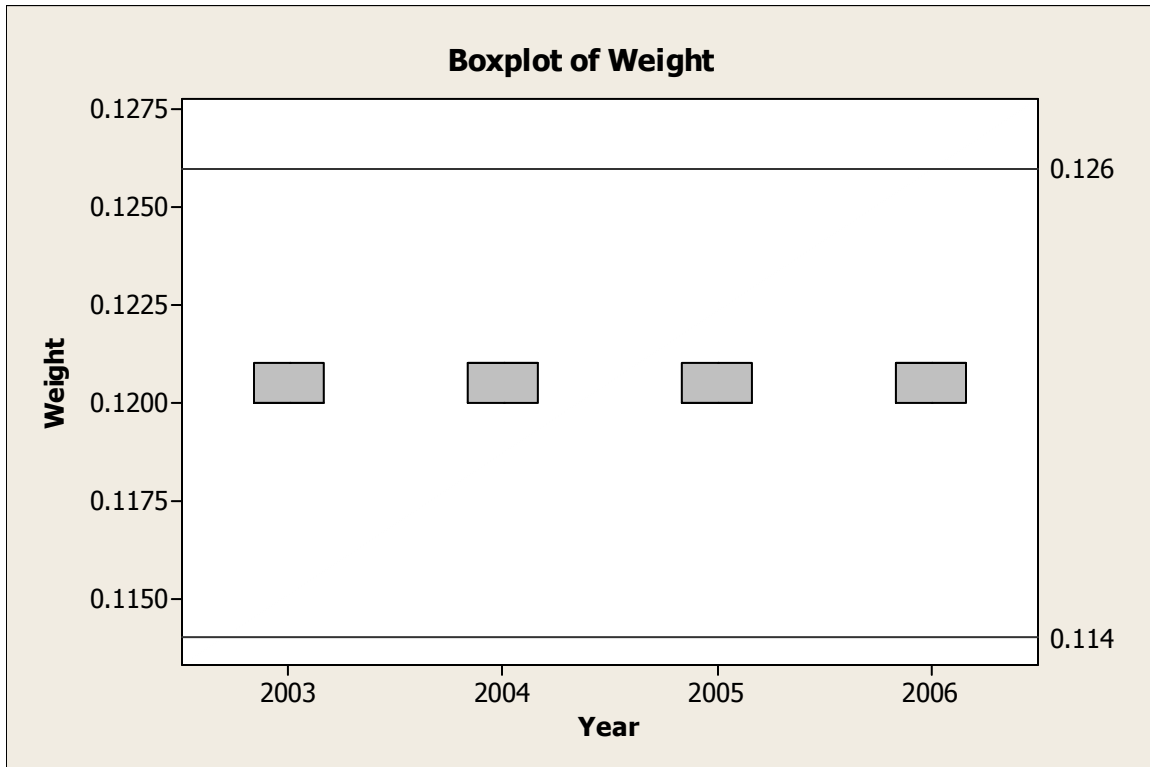


Figures 8-14 0.25mg Dose
Boxplots of Batch Variation Within and Between Years 2003 – 2006

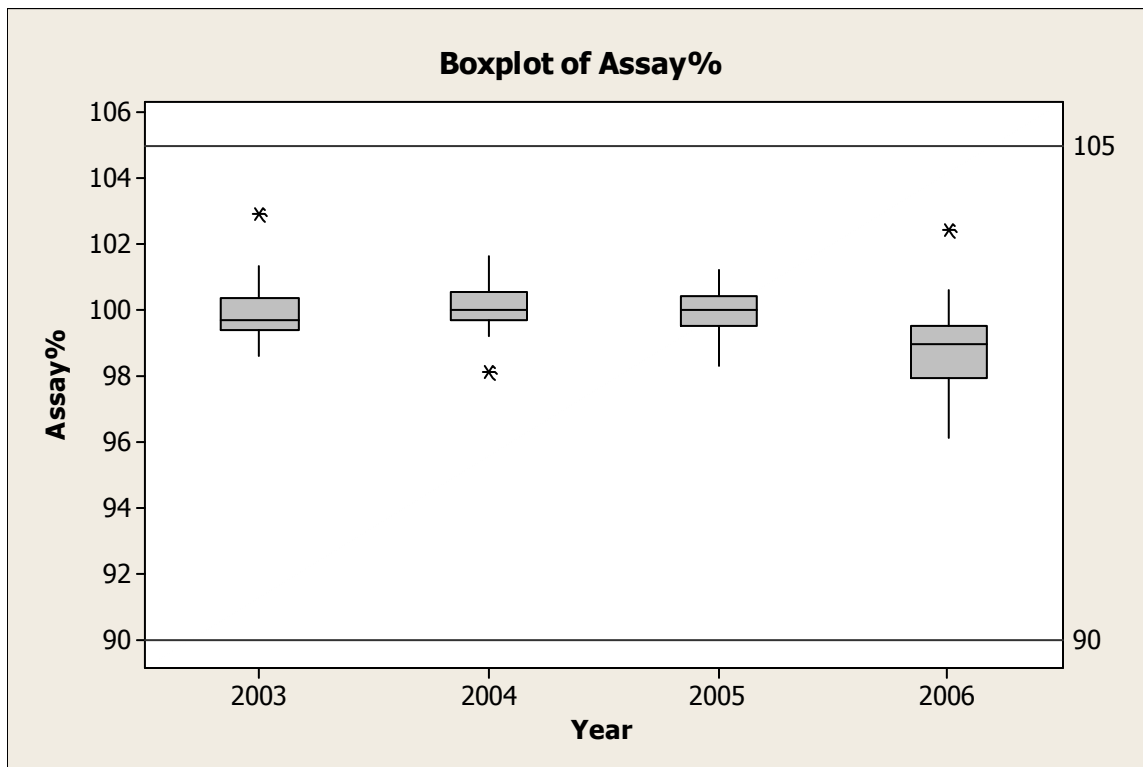
Figures 8-9. Blend Assay and Blend Assay Uniformity (RSD)

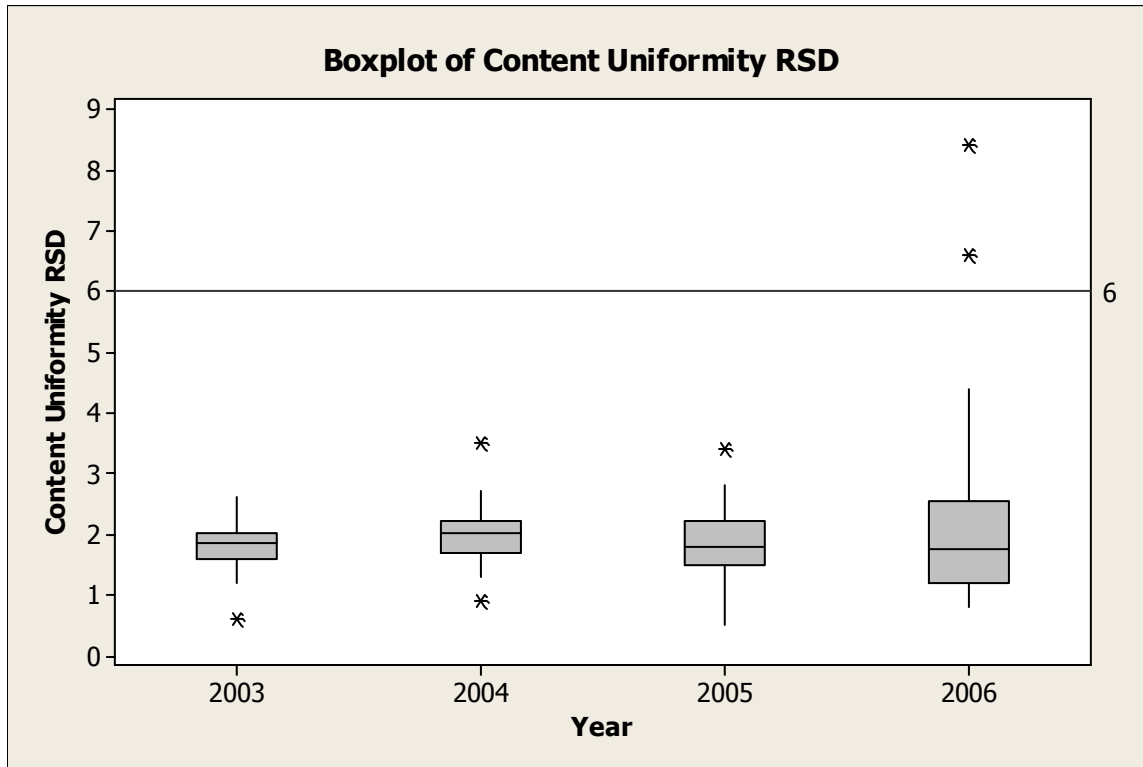


Figures 10-11. Batch Average Tablet Weight and Hardness



Figures 12-13. Batch Average Tablet Thickness and Assay %



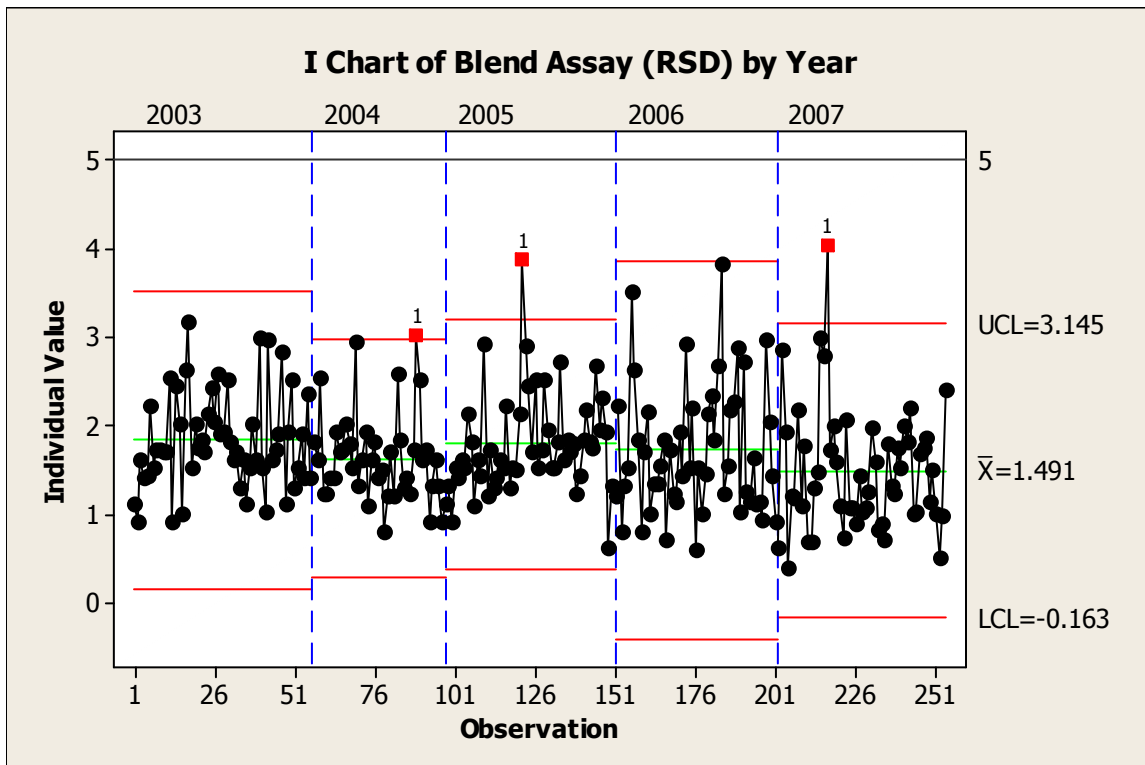
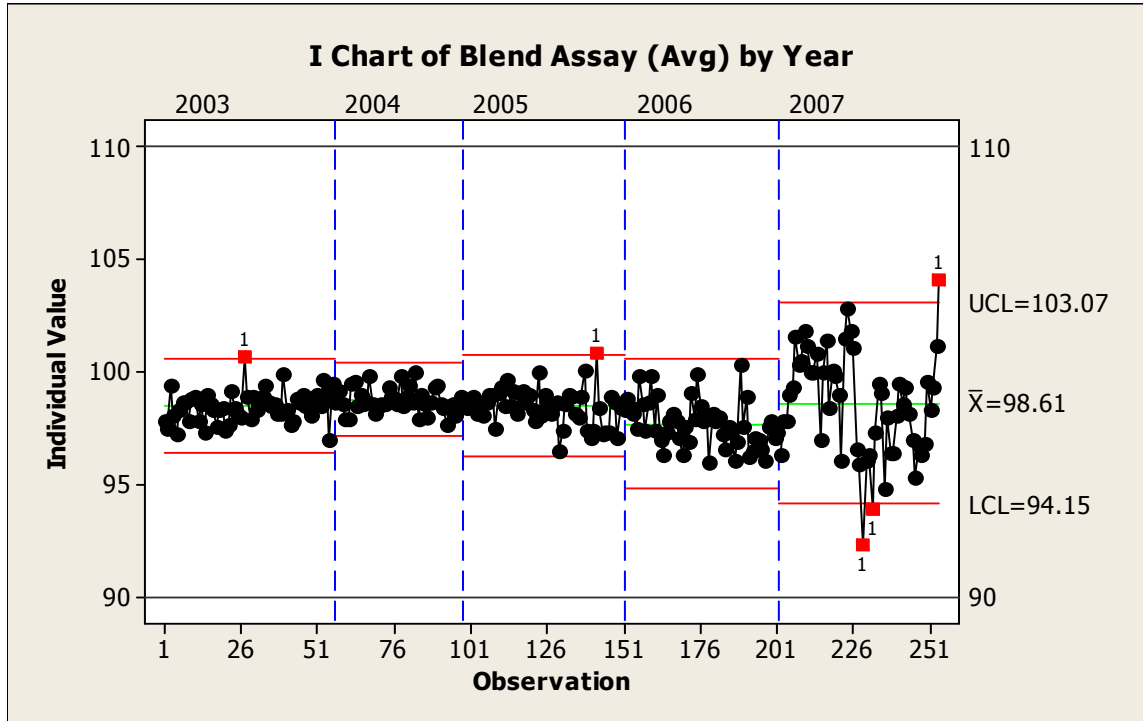
Figures 14. Batch Tablet Content Uniformity RSD

Time Series Plots

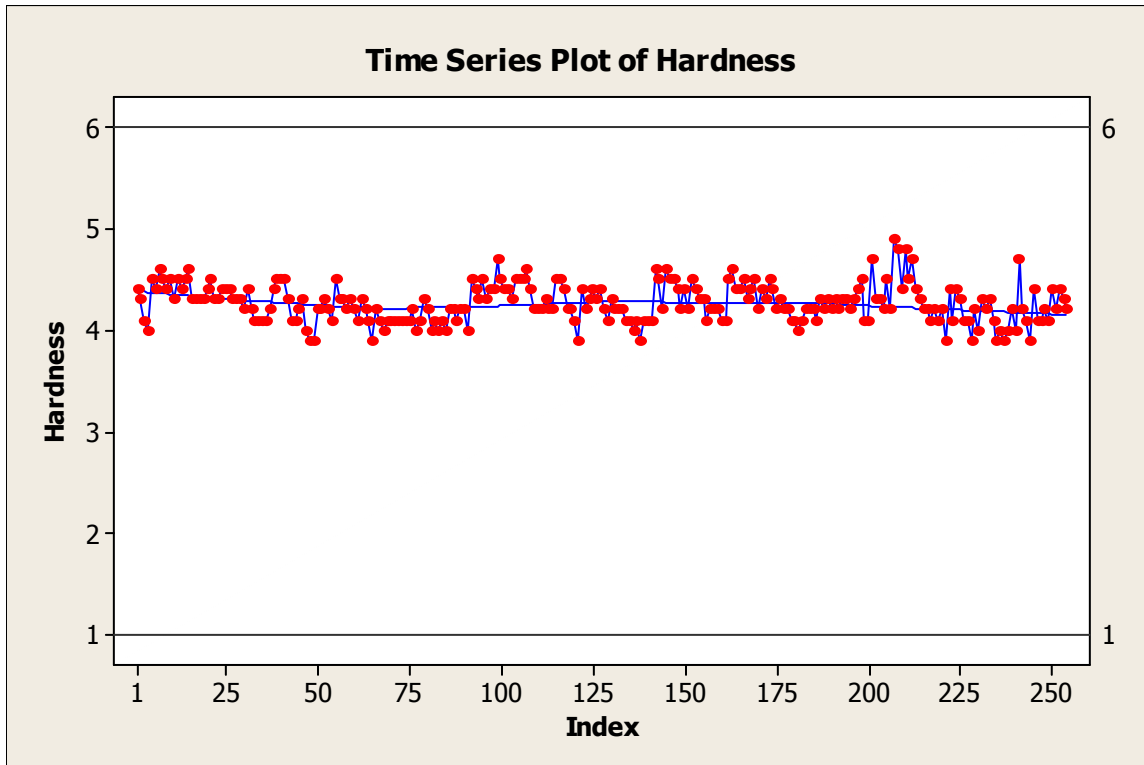
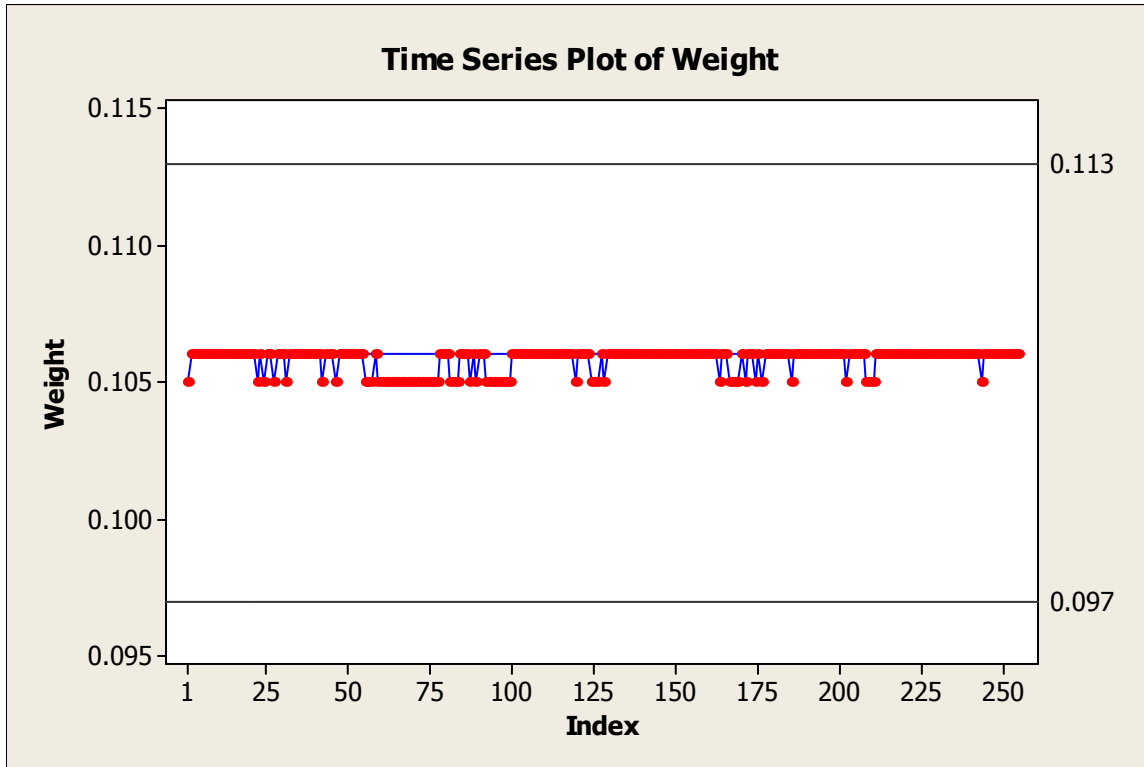
The following time series plots show the batch parameters (weight, hardness, thickness, assay and content uniformity) plotted in sequence to provide another view of the batch-to-batch consistency over time

**Figures 15-21. 0.125mg Dose
Time Series Plots of Batch Trends 2003 – 2007**

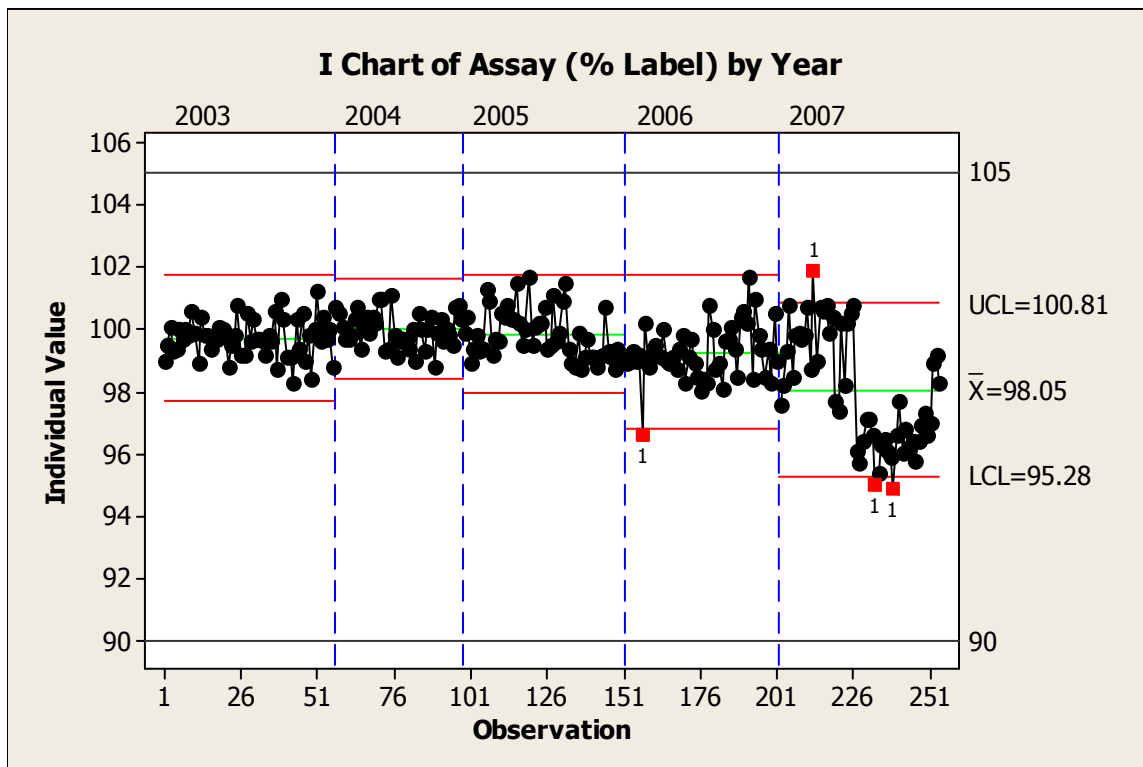
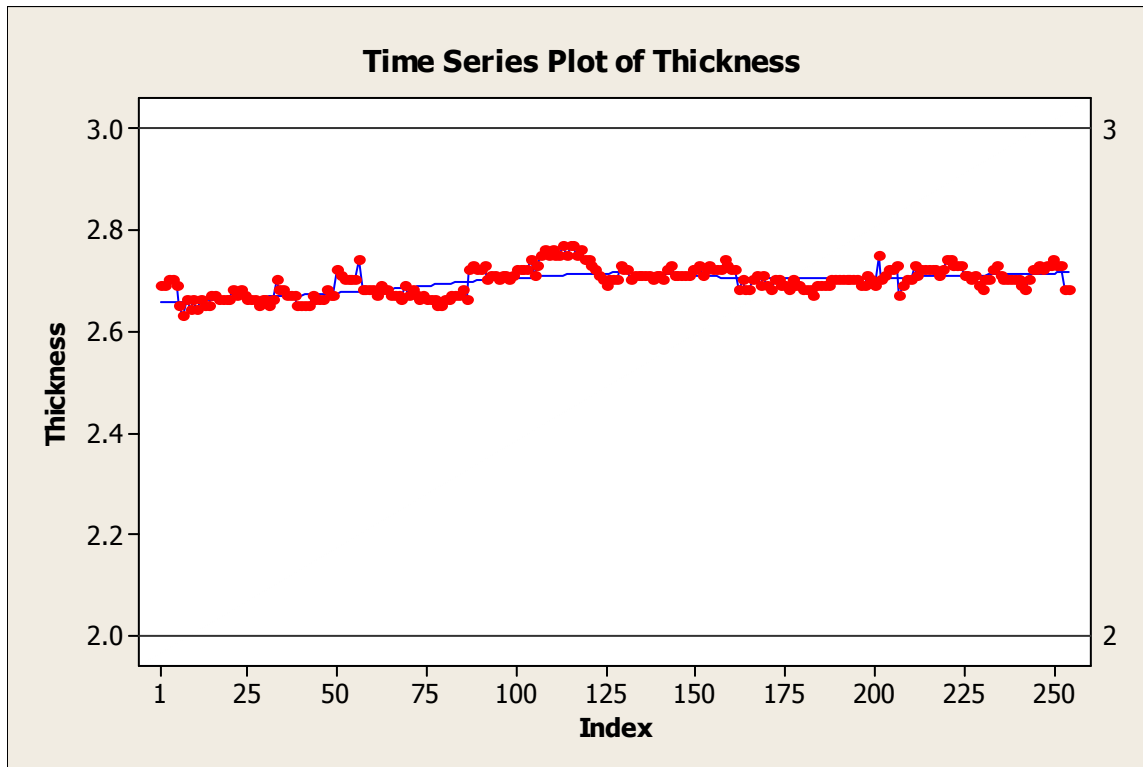
Figures 15-16. Blend Assay and Blend Assay Uniformity RSD



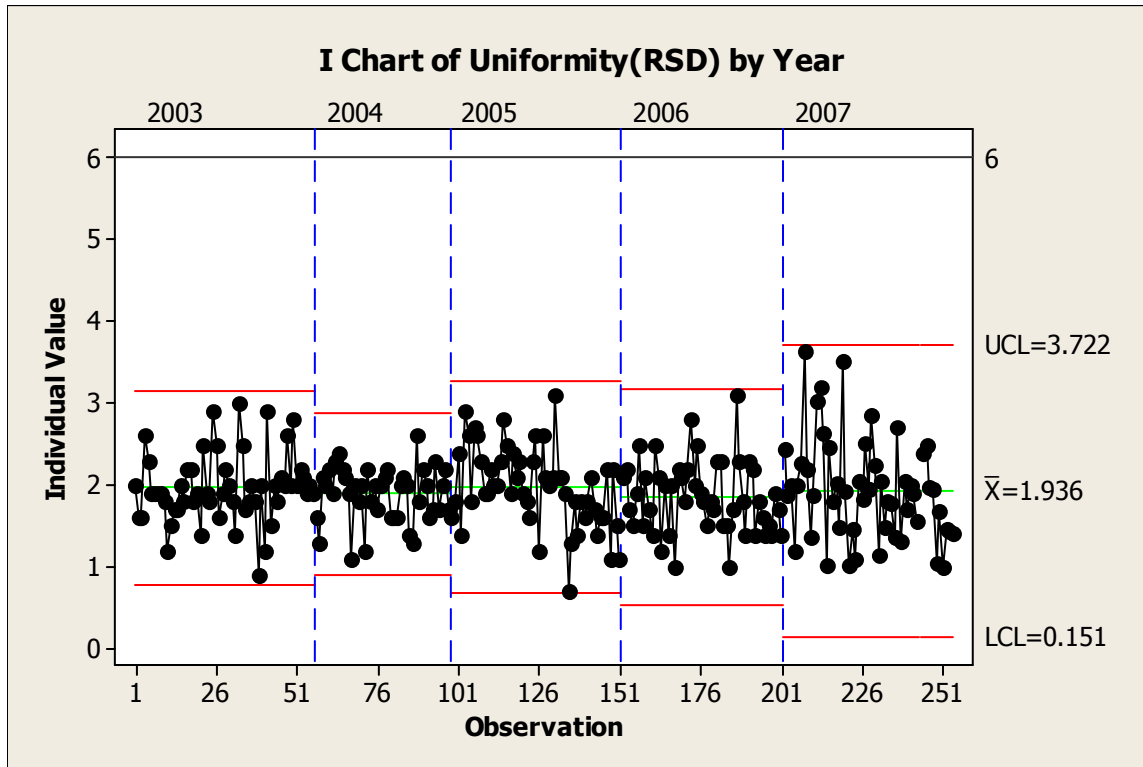
Figures 17-18. Batch Average Tablet Weight and Hardness



Figures 19-20. Batch Average Tablet Thickness and Assay

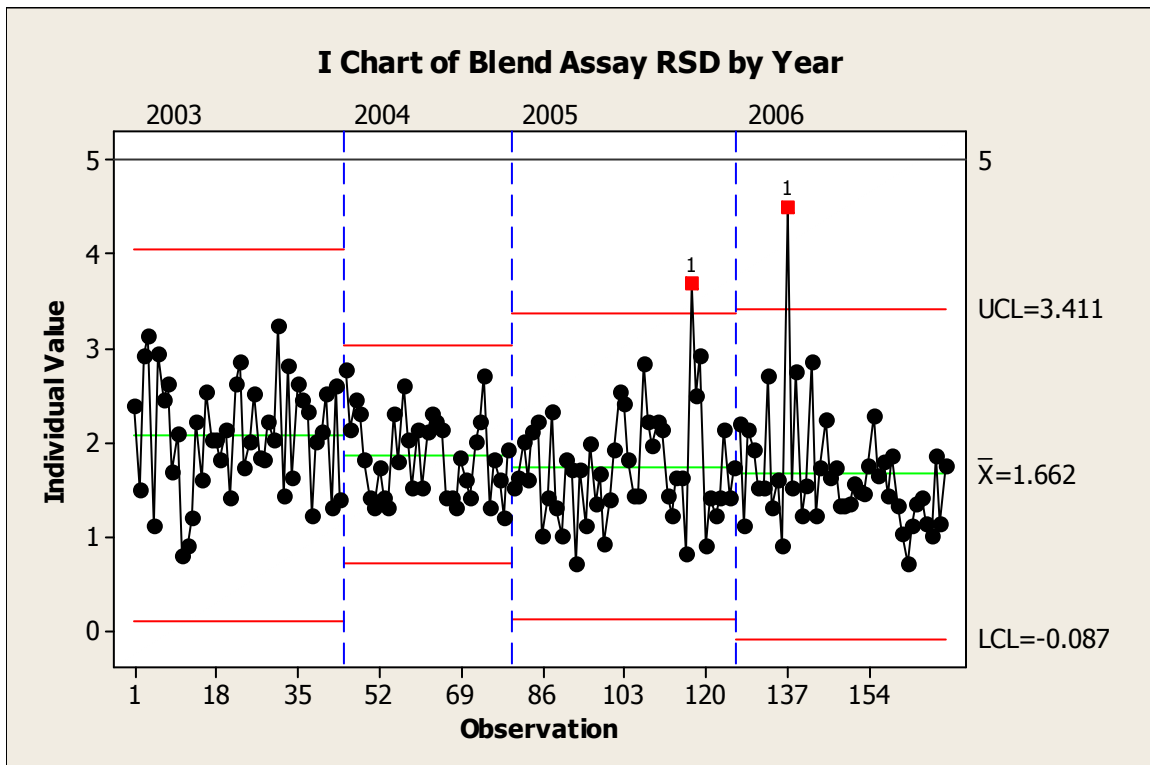
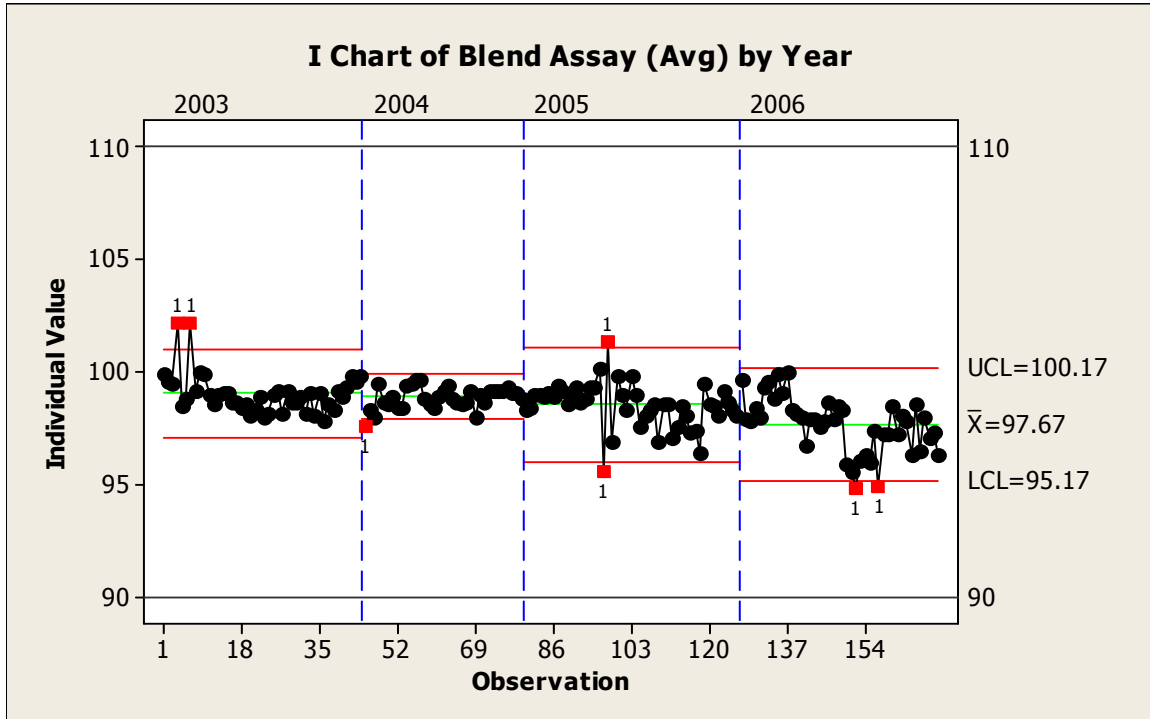


Figures 21. Batch Tablet Content Uniformity RSD

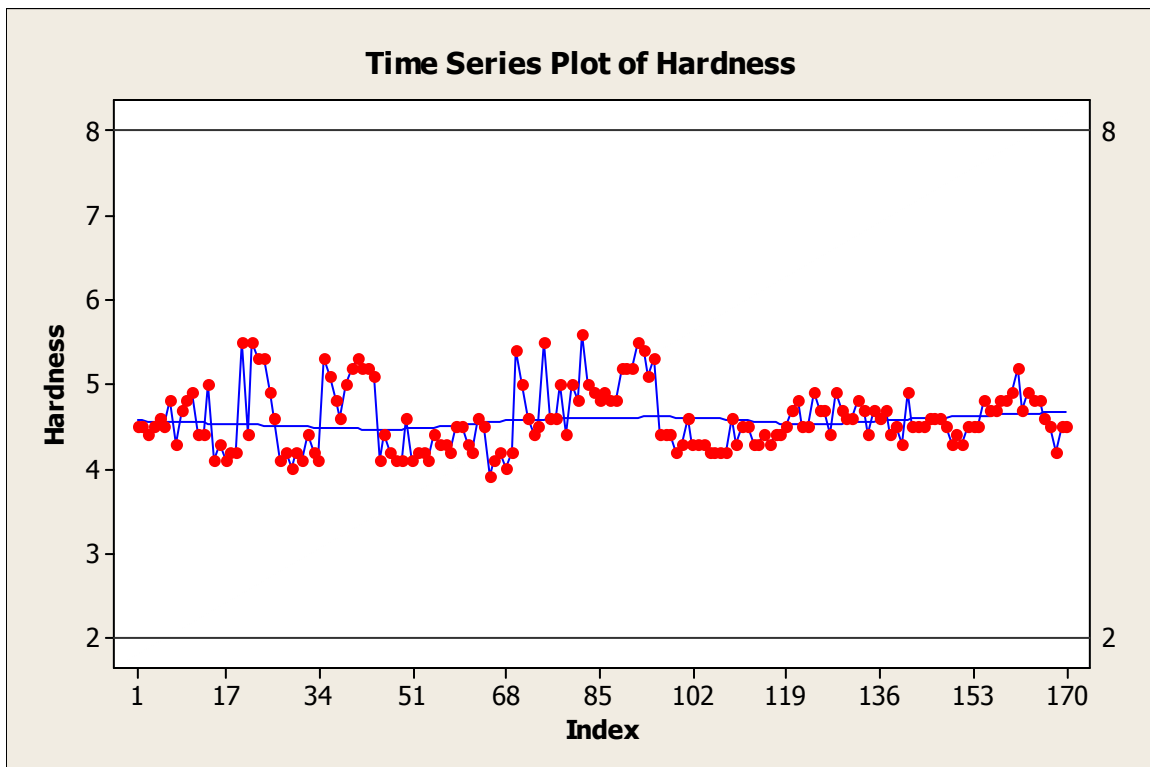
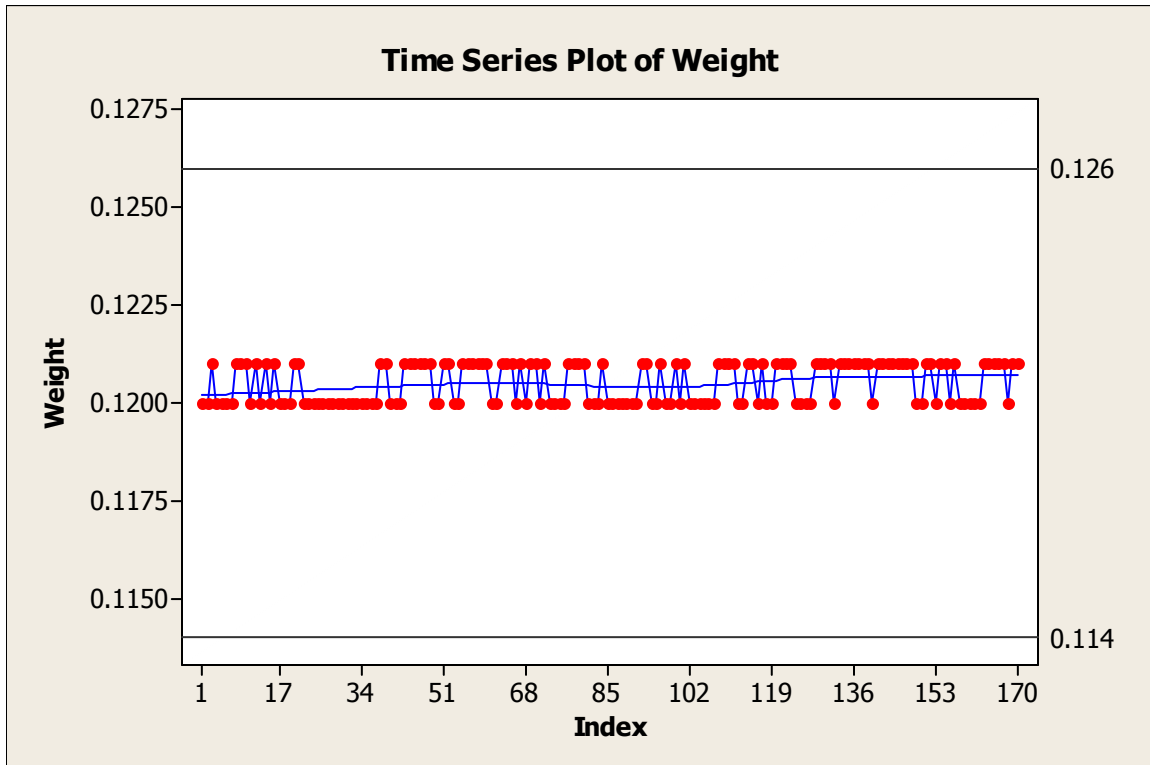


**Figures 22-28. 0.25mg Dose
Time Series Plots of Batch Trends 2003 – 2007**

Figures 22-23. Blend Assay and Blend Assay Uniformity RSD



Figures 24-25. Batch Average Tablet Weight and Hardness



Figures 26-27. Batch Average Tablet Thickness and Assay

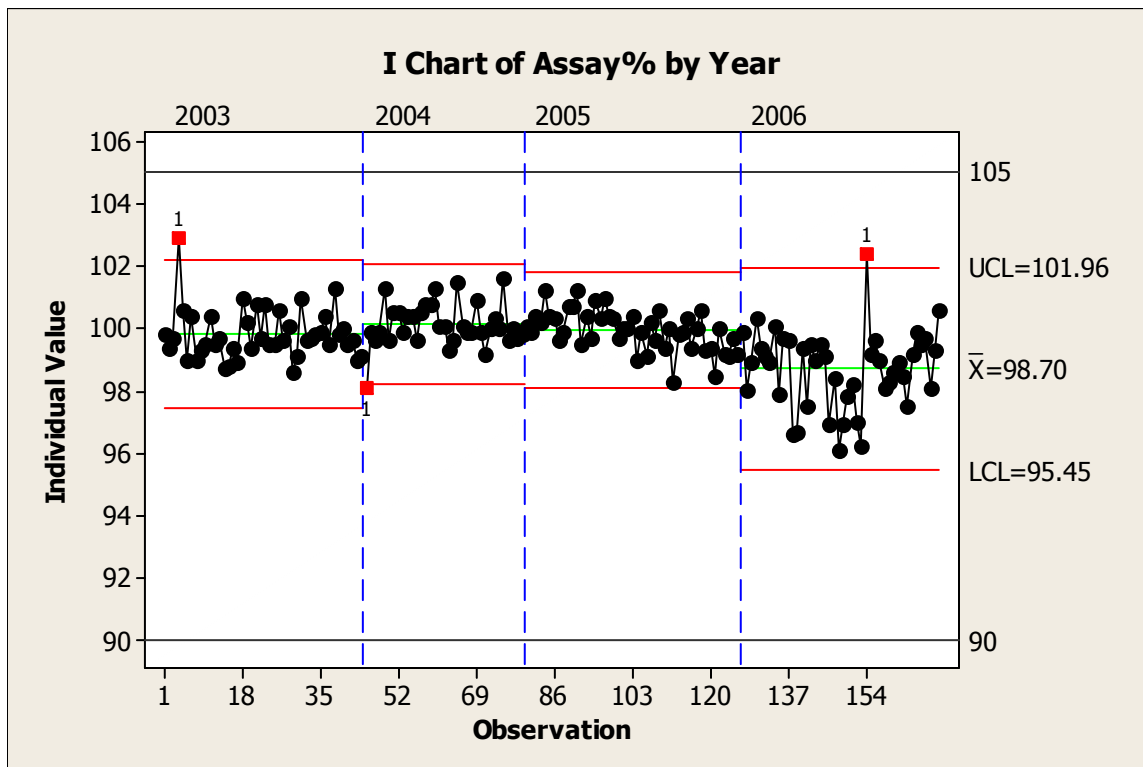
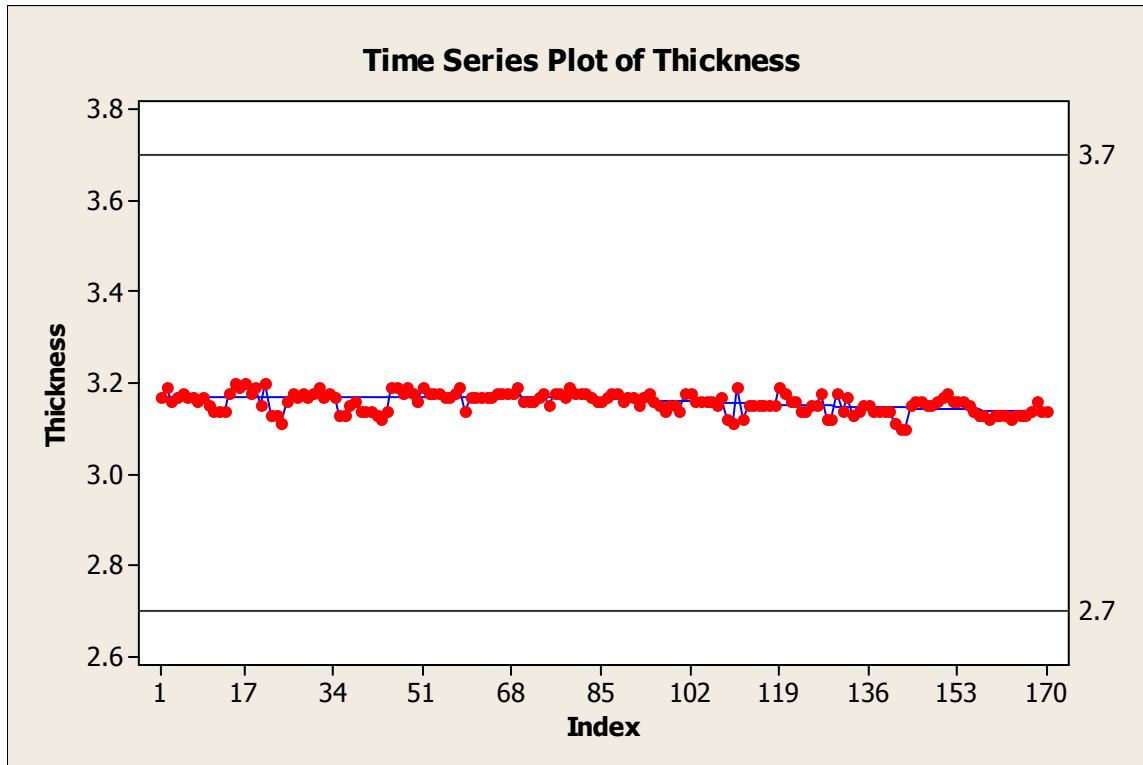
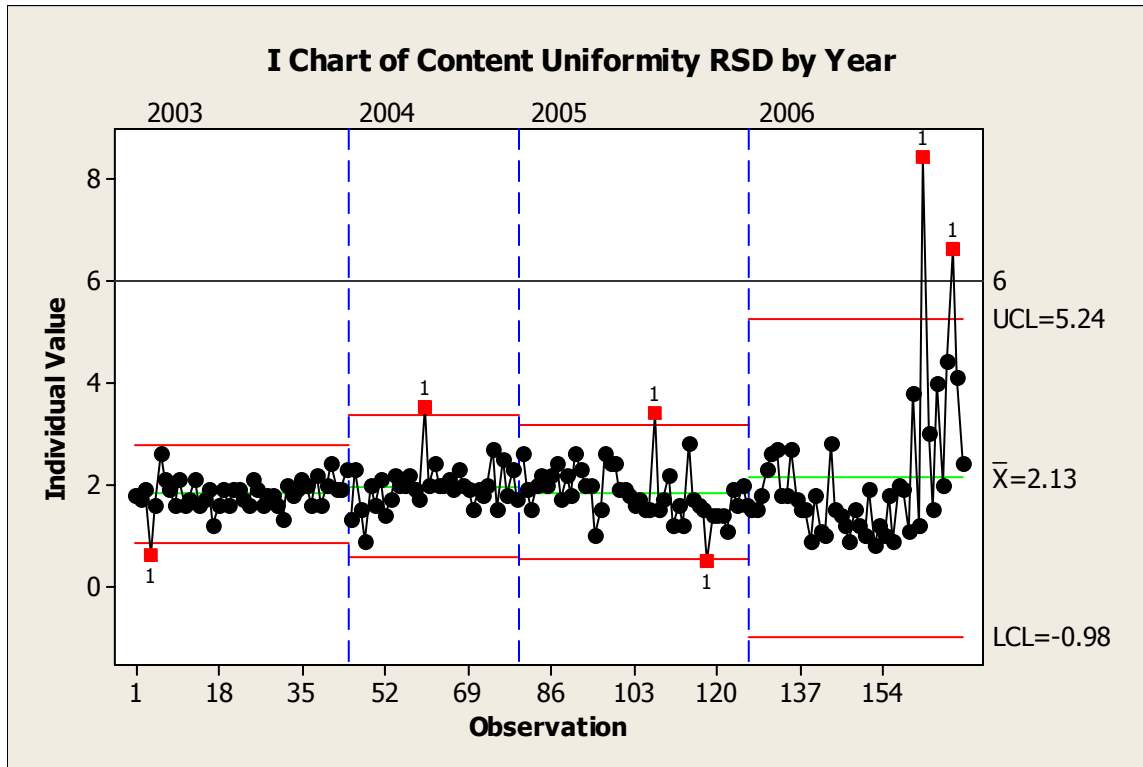


Figure 28. Batch Tablet Content Uniformity (RSD)

Figures Supporting the Analysis of Batch 70924A Results

Figures 29-30

Plots of Tablet Weight and Hardness for the Manufacture of Batch 70924A
Data Collected by QA during Batch Production

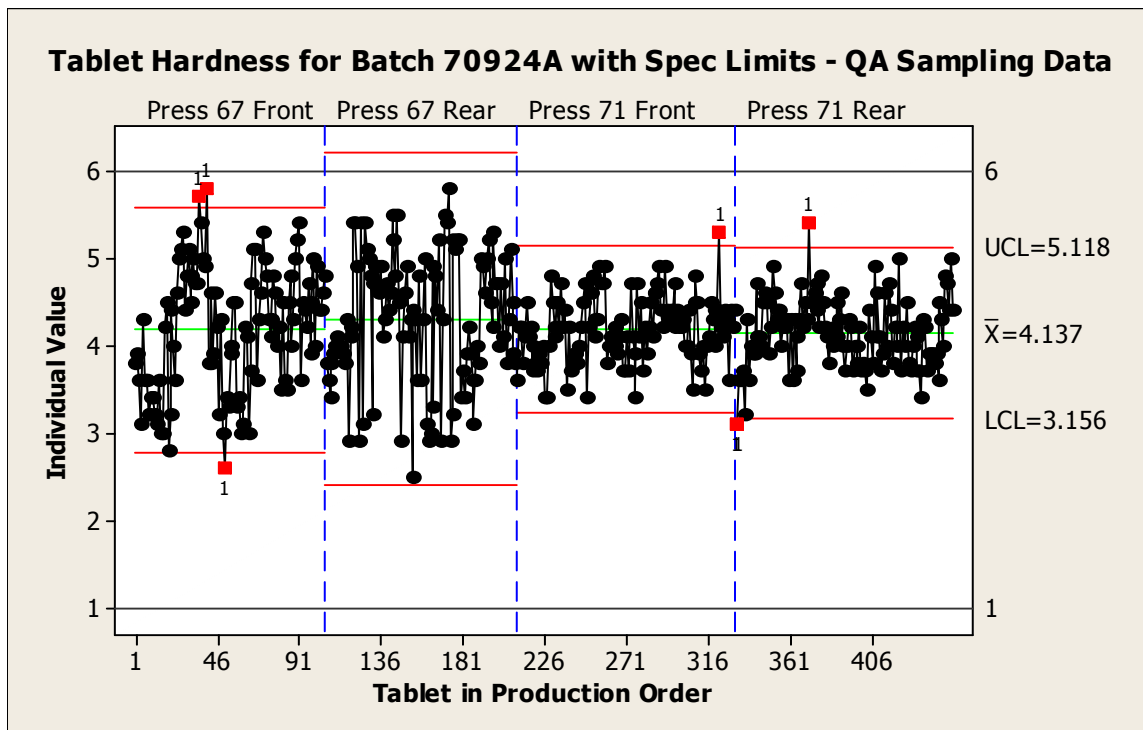
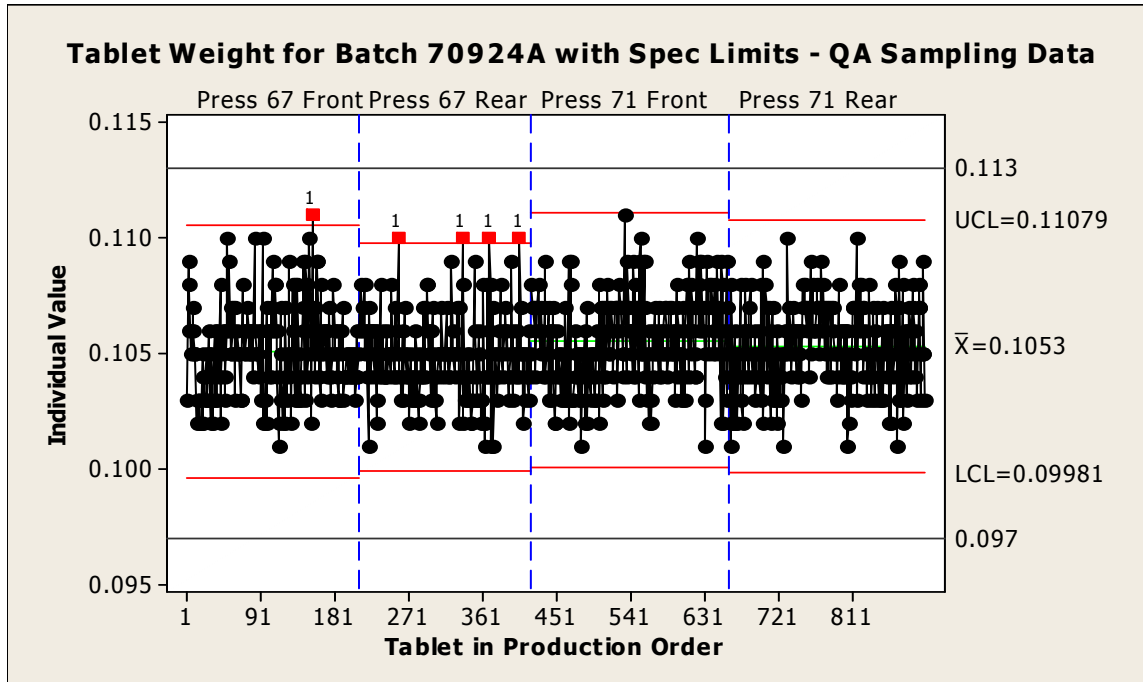
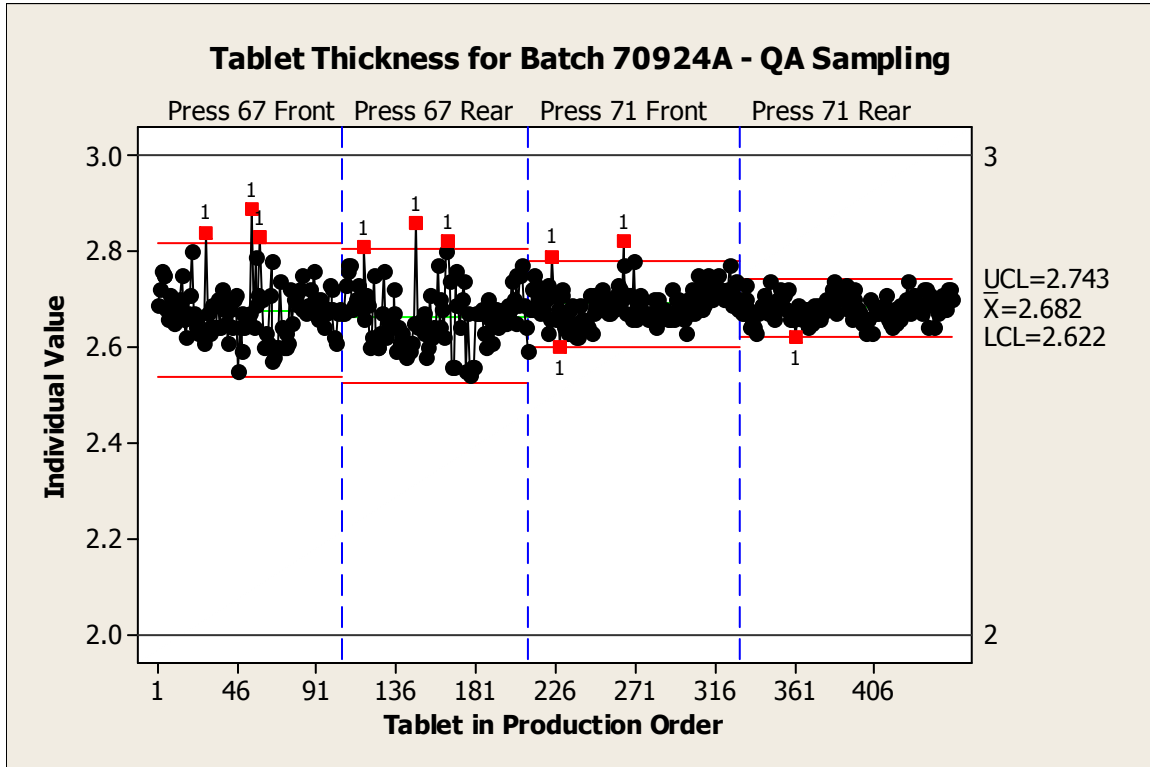


Figure 31

Plot of Tablet Thickness for the Manufacture of Batch 70924A
Data Collected by QA during Batch Production



Figures 32-33

Plots of Tablet Weight and Hardness for the Manufacture of Batch 70924A
Data Collected by Process Operators during Batch Production

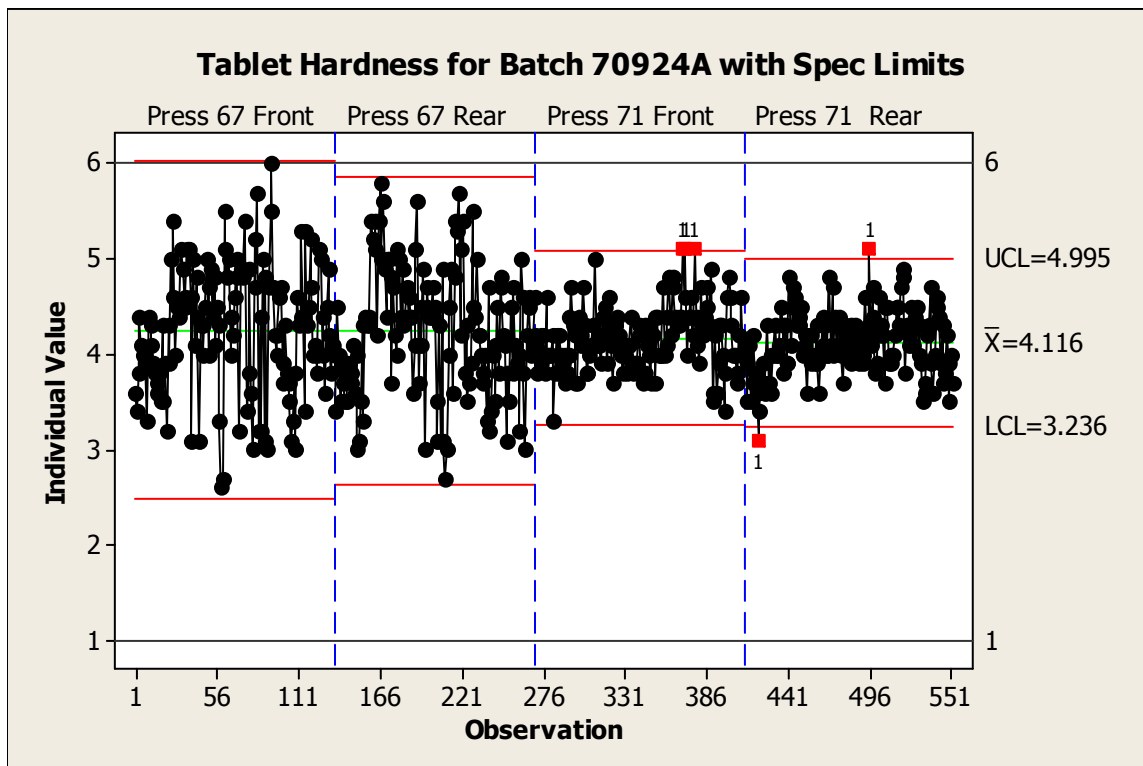
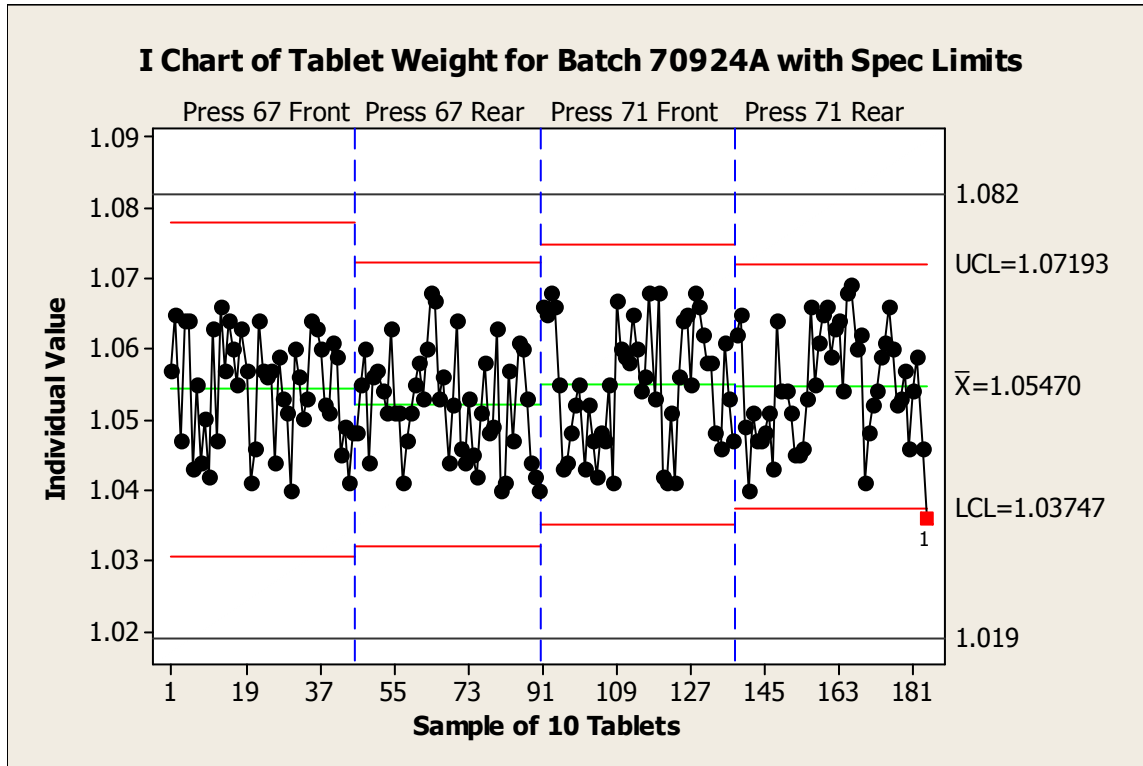
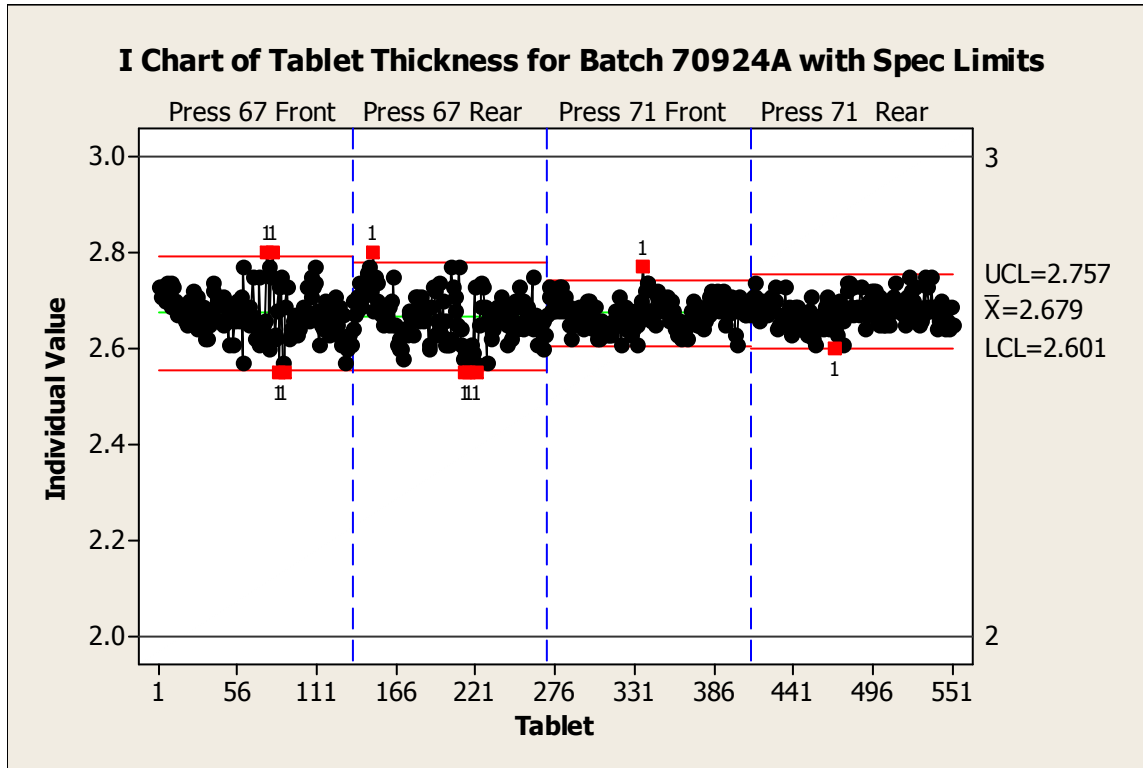


Figure 34
Plot of Tablet Thickness for the Manufacture of Batch 70924A
Data Collected by Process Operators during Batch Production



Figures 35-36

Plots of Tablet Weight and Hardness for the Manufacture of Batch 70924A
Data Collected by Process Operators and QA during Batch Production

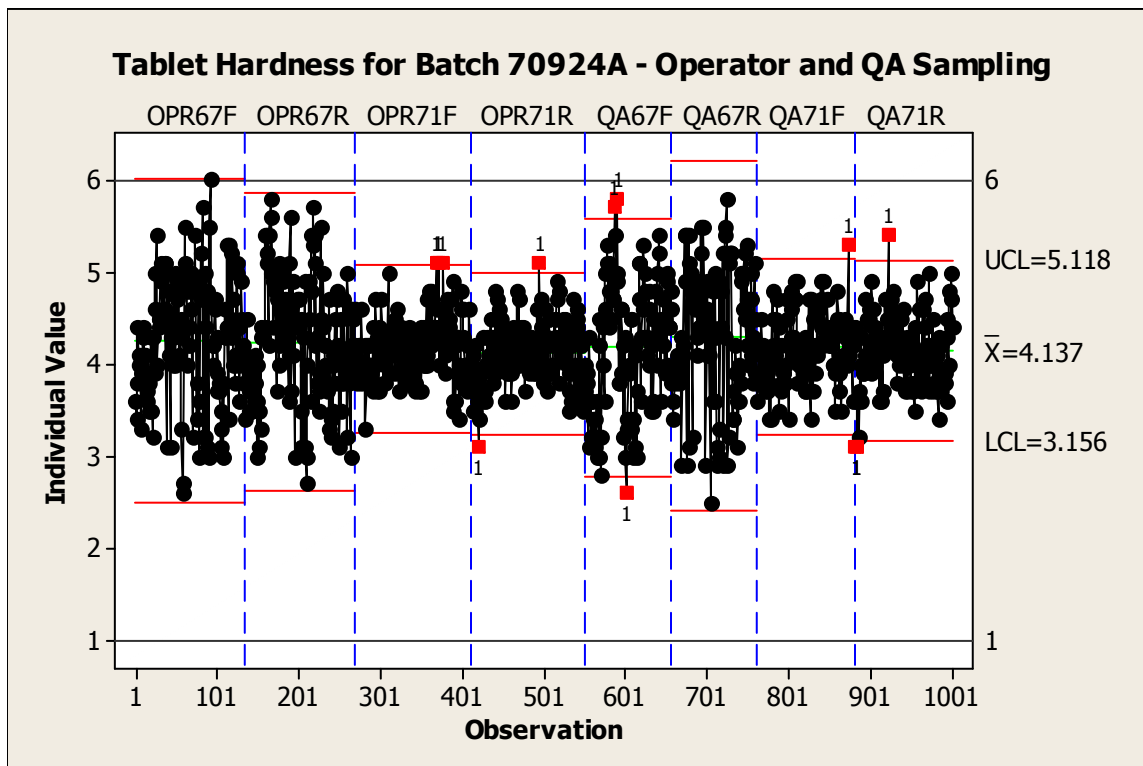
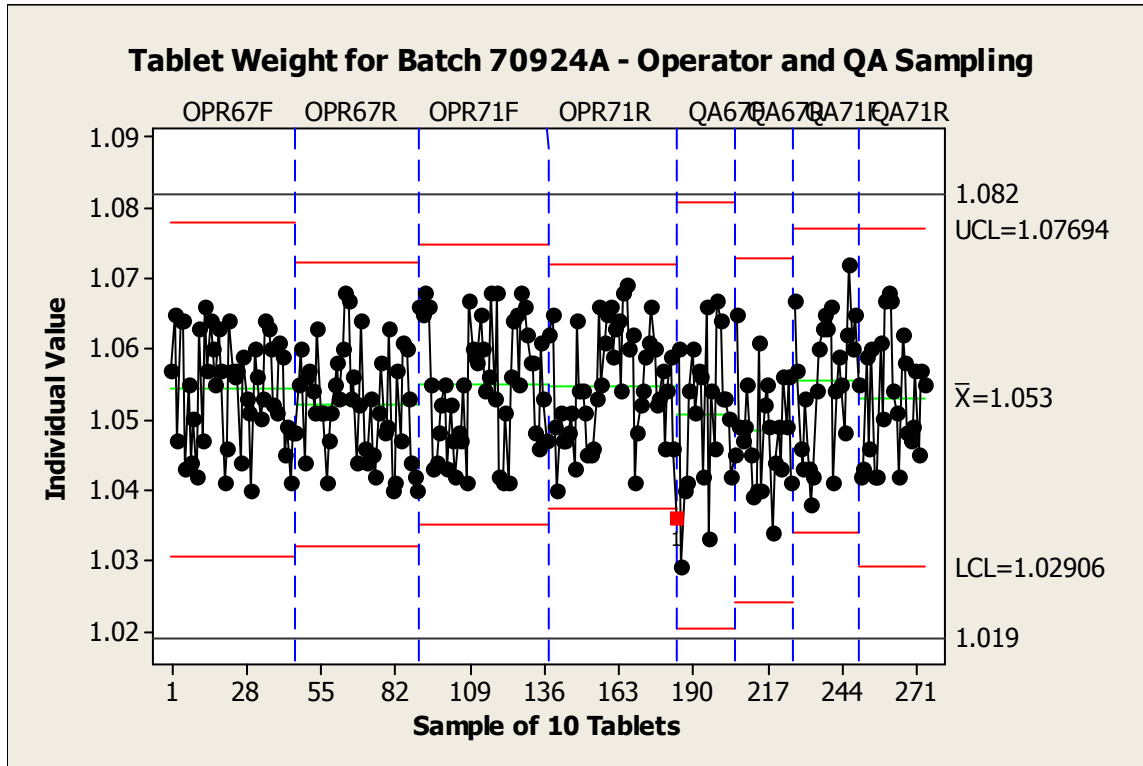
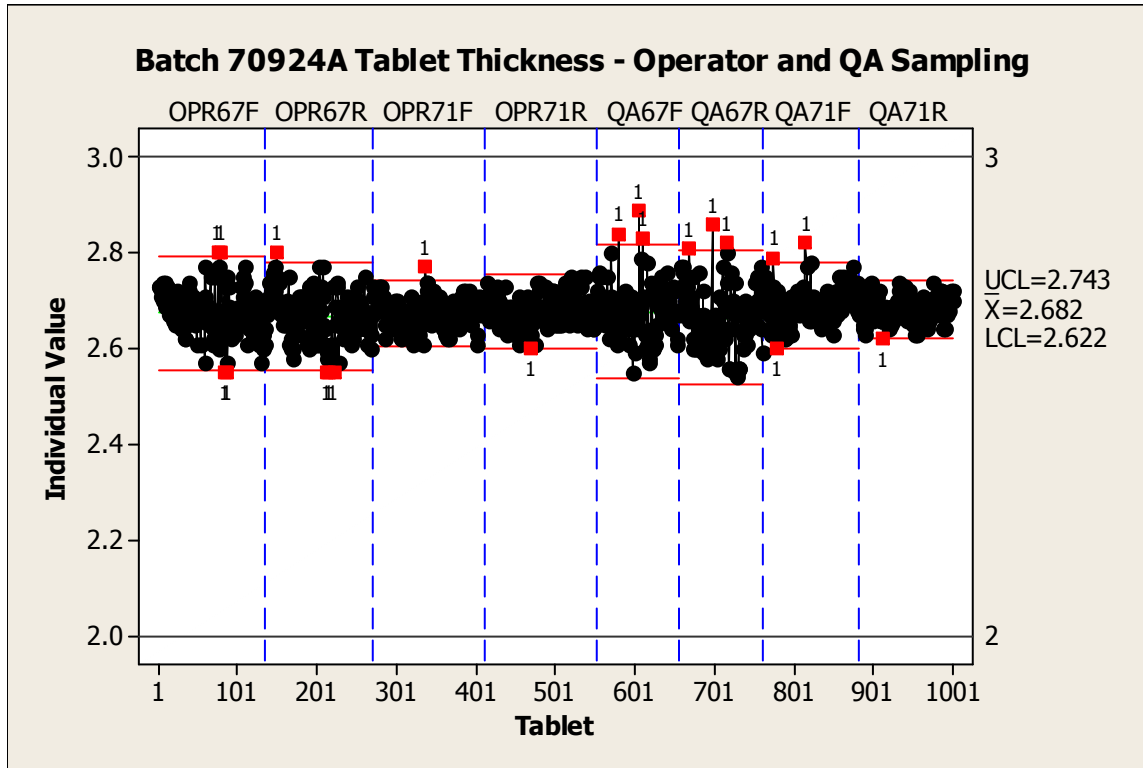
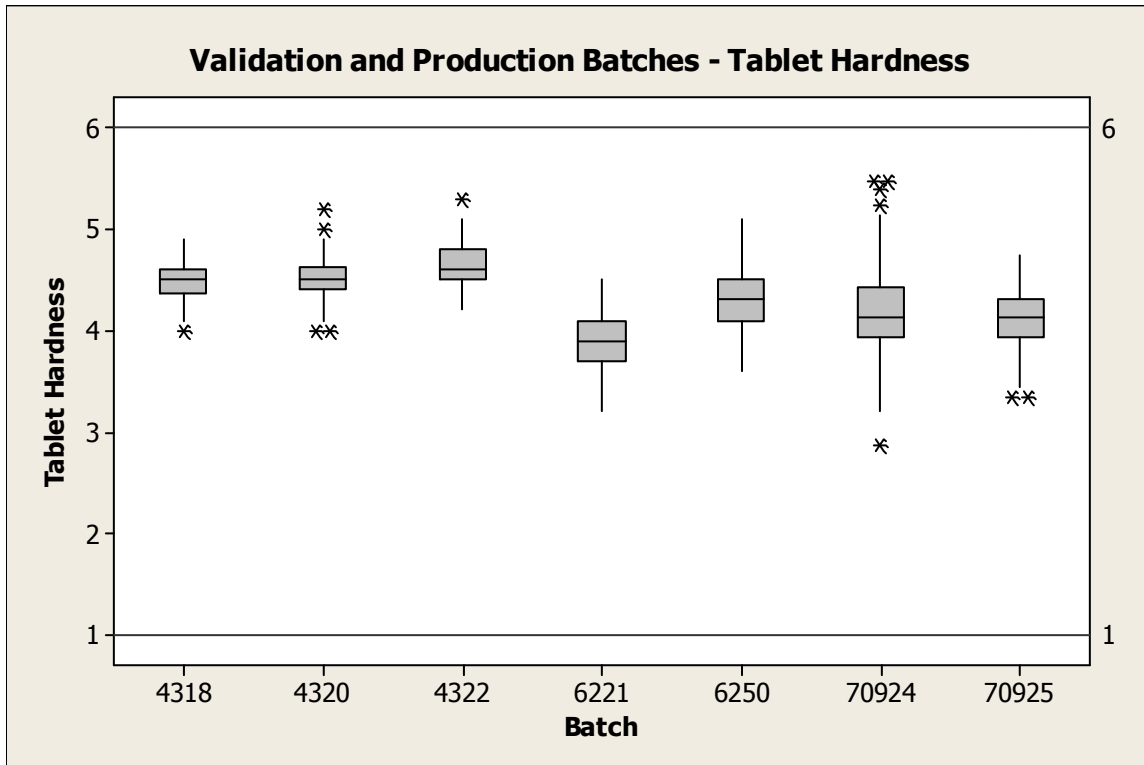
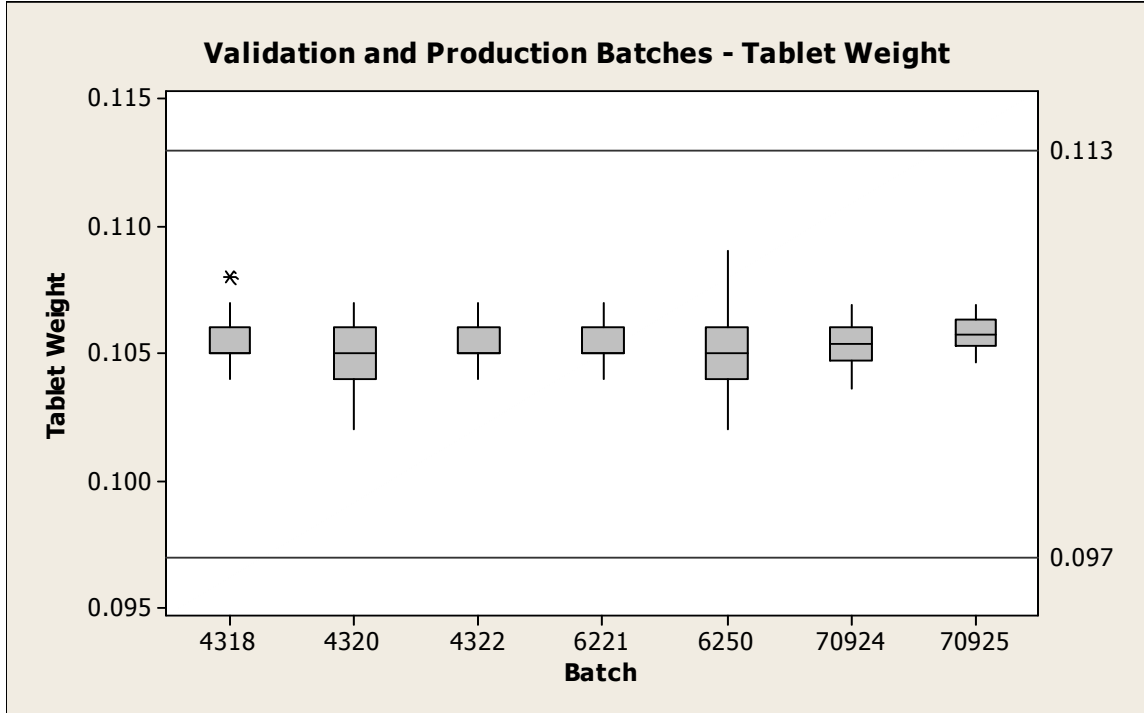
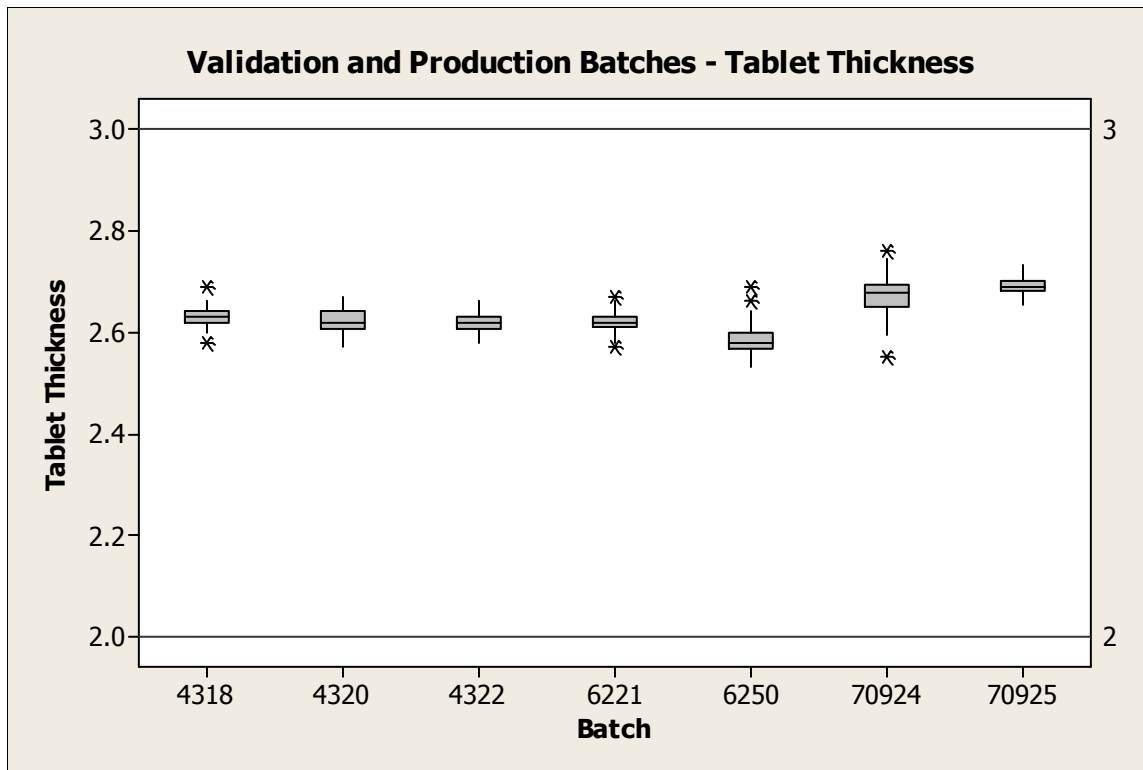


Figure 37
Plot of Tablet Thickness for the Manufacture of Batch 70924A
Data Collected by Process Operators and QA during Batch Production

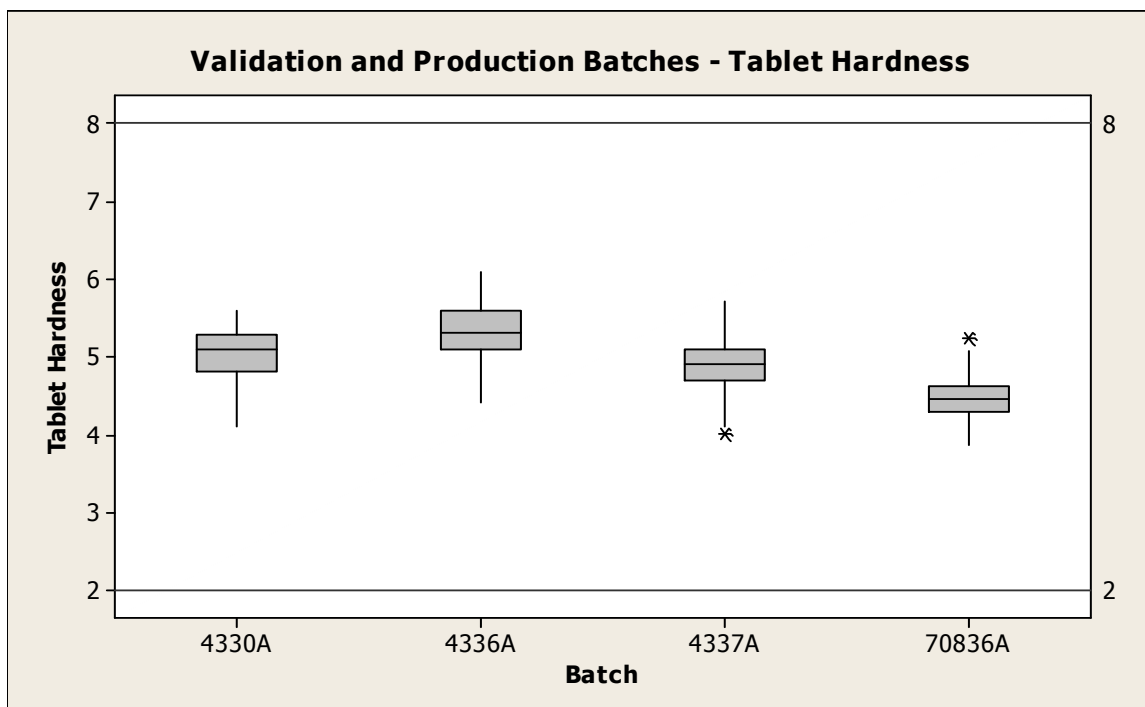
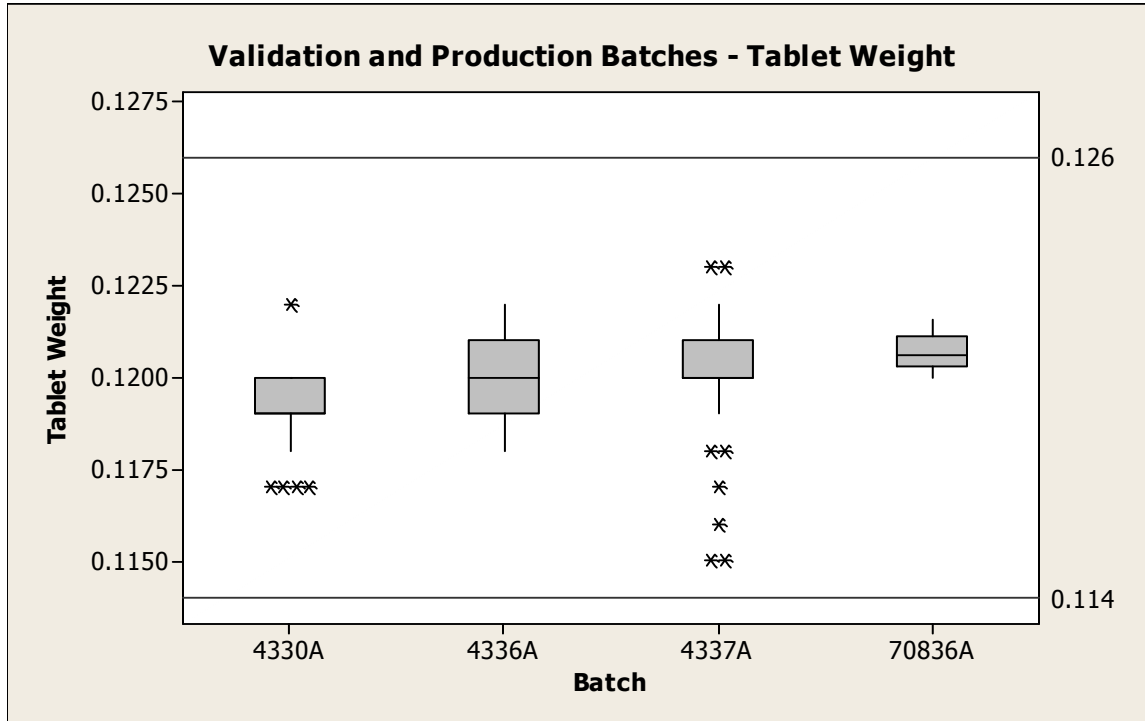


Figures 38, 39 and 40
0.125mg Dose - Validation and Production Batch Comparison
Validation Batches 4318A, 4320A, 4322A, 6221A and 6250A;
Production Batches 70924A and 70925A





Figures 41, 42 and 43
0.25mg Dose - Validation and Production Batch Comparison
Validation Batches 4330A, 4336A and 4337A
Production Batch 70836A



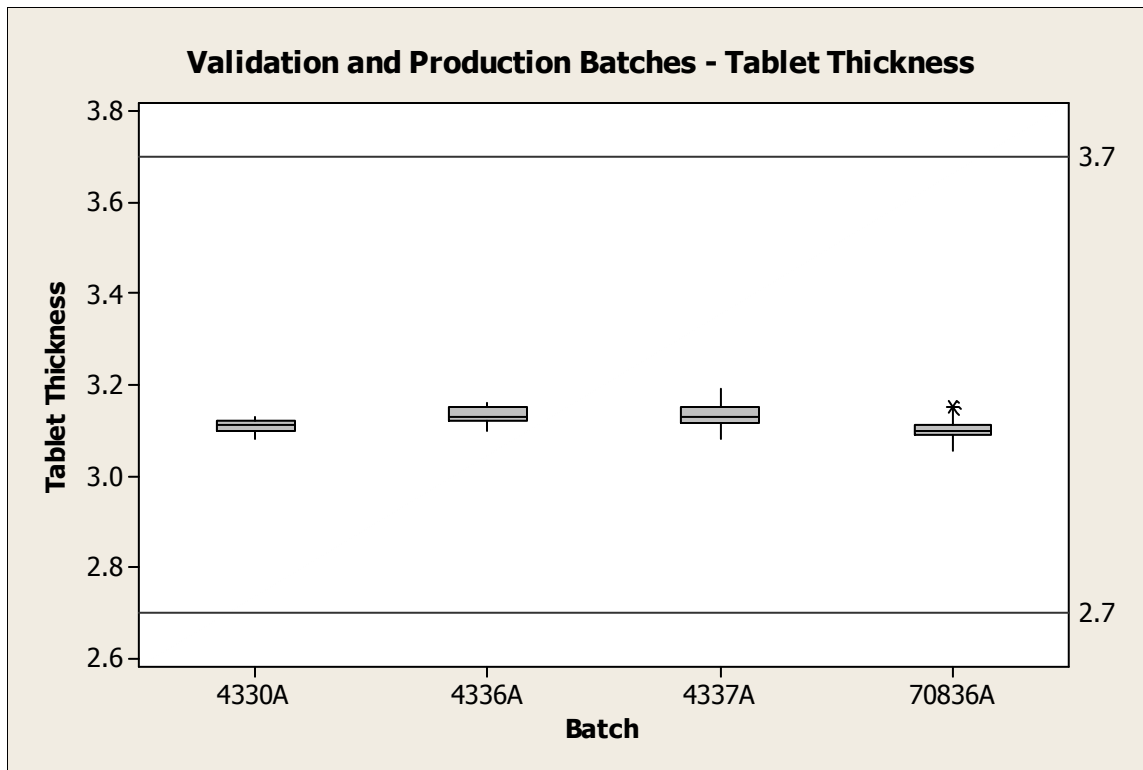


Table 1 - 0.125mg Dose Batch Trend Analysis 2003-2007

Parameter	ANOVA p-Value	Variation (%) Explained by Year	Kruskall- Wallis p-Value	Mood's Median p-Value
Blend Assay (Avg)	0.001	5.6	0.000	0.000
Blend Uniformity (RSD)	0.037	2.5	0.008	0.108
Weight	0.000	29.6	0.001	0.000
Hardness	0.005	4.2	0.002	0.002
Thickness	0.000	51.3	0.000	0.000
Assay	0.000	28.8	0.000	0.000
Content Uniformity (RSD)	0.662	0.0	0.573	0.668
Weight Uniformity (SD)	0.000	7.9	0.000	0.000
Hardness Uniformity (SD)	0.000	9.6	0.000	0.009
Thickness Uniformity (SD)	0.000	20.0	0.000	0.000

Nature of Observed Trend

Blend Assay (Avg)	2006 Average is 0.9% lower than other years
Blend Uniformity RSD	2007 Average is 13.8% lower than other years
Weight	2004 Average is 0.4% lower than other years
Hardness	2004 Average is 1.8% lower than other years
Thickness	Upward trend 2003 -2007;2007 is 1.6% higher than 2003
Assay	2007 Average is 1.3% lower than other years
Content Uniformity (RSD)	Downward Trend Not Significant - 2006 and 2007 RSD Lower
Weight Uniformity (SD)	2007 Average is 14.8% higher than other years
Hardness Uniformity (SD)	2006 Average is 7.9% lower than other years
Thickness Uniformity (SD)	Downward Trend - 2006 and 2007 lower

Table 2A - 0.125mg Dose Batch Trend Analysis 2003 - 2007 by Year

<u>Parameter</u>	<u>Statistic</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>	<u>2007</u>
Number of Batches		56	42	53	50	53
Blend Assay(Avg)	Stability	Stable	Stable	Stable	Stable	Not Stable
	Ppk	4.05	5.39	3.46	2.47	1.21
	Out of Specification %	0	0	0	0	0
	Long-Term Variation %	2.6	0.5	16.2	16	60.5
-	-					
Blend Assay RSD	Stability	Stable	Stable	Stable	Stable	Stable
	Ppk	1.94	2.23	1.88	1.47	1.68
	Out of Specification %	0	0	0	0	0
	Long-Term Variation %	0	21.6	30.9	8.3	37.1
Weight	Stability	Stable	Stable	Stable	Stable	Stable
Hardness	Stability	Stable	Stable	Stable	Stable	Stable
Thickness	Stability	Stable	Stable	Stable	Stable	Stable
Assay (% of Label)	Stability	Stable	Stable	Stable	Stable	Not Stable
	Ppk	2.85	2.96	2.18	2.16	1.23
	Out of Specification (%)	0	0	0	0	0
	Long-Term Variation (%)	16.2	10.8	36.4	12.9	75.9
Uniformity RSD	Stability	Stable	Stable	Stable	Stable	Stable
	Ppk	3.18	4.09	2.72	3.13	1.81
	Out of Specification (%)	0	0	0	0	0
	Long-Term Variation (%)	11.1	2.2	23.3	1.0	17.3
Weight SD	Stability	Stable	Stable	Stable	Stable	Stable
Hardness SD	Stability	Stable	Stable	Stable	Stable	Stable
Thickness SD	Stability	Stable	Stable	Stable	Stable	Stable

Table 2B - Batch Trends 0.125mg Dose 2008 - With Years 2006 - 2007 for Comparison

Parameter	Statistic	Specification	2008 APR Result	2007 APR Result	2006 APR Result
Batches	Number		18	50	53
Average Blend Assay	Average		99.0	98.6	97.7
	Range	90-110	94.1-103.1	92.3-104.1	95.9-100.3
	Out of Specification %		0	0	0
Blend Assay RSD	Average		1.4	1.5	1.7
	Range	< 5%	0.7 - 2.3	0.4 - 4.0	0.6 - 3.8
	Out of Specification %		0	0	0
Tablet Weight	Average		0.106	0.106	0.106
	Range	0.097 - 0.113	0.1 - 0.111	0.101 - 0.112	0.100 - 0.111
	Out of Specification %		0	0	0
Tablet Hardness	Average		4.3	4.2	4.3
	Range	1.0 - 6.0	3.0 - 5.7	2.5 - 6.3	2.00 - 2.85
	Out of Specification %		0	NA	0
Tablet Thickness	Average		2.71	2.71	2.7
	Range	2.00 - 3.00	2.55 - 2.90	2.20 - 2.89	2.00 - 2.85
	Out of Specification %		0	0	0
Assay (% of Label)	Average		98.8	98.0	99.3
	Range	90 - 105	95.7 - 102.2	94.5 - 101.9	96.5 - 101.7
	Out of Specification %		0	0	0
Content Uniformity AV	Average		4.3	4.8	4.8
AV = Acceptance Value	Range	< 15%	1.1 9.2	2.4 - 11.3	2.5 - 7.8
	Out of Specification %		0	0	0

Table 3 - Dose 0.25 Batch Trend Analysis 2003-2006

Parameter	ANOVA p-Value	Variation (%) Explained by Year	Kruskall- Wallis p-Value	Mood's Median p-Value
Blend Assay (Avg)	0.000	22.5	0.000	0.000
Blend Uniformity RSD	0.008	5.2	0.002	0.009
Weight	0.000	9.9	0.000	0.000
Hardness	0.009	5.1	0.002	0.040
Thickness	0.000	25.4	0.000	0.000
Assay	0.000	27.1	0.000	0.000
Content Uniformity (RSD)	0.284	0.5	0.276	0.117
Weight Uniformity (SD)	0.000	46.7	0.000	0.000
Hardness Uniformity (SD)	0.000	15.6	0.000	0.000
Thickness Uniformity (SD)	0.000	23.5	0.000	0.000

Nature of Observed Trend

Blend Assay (Avg)	2006 Average 1.2% lower than other years
Blend Uniformity RSD	RSD Decreases - 2006 Average is 20.7% lower than 2003
Weight	2006 Average 0.3% higher than 2003 average
Hardness	2004 Average is 4.3% lower than other years
Thickness	2006 Average 0.8% less than other years
Assay	2006 Average 1.3% less than other years
Content Uniformity (RSD)	2006 Average 17.6% higher than other years
Weight Uniformity (SD)	2006 Average SD is lower
Hardness Uniformity (SD)	2006 Average SD is lower
Thickness Uniformity (SD)	2006 Average SD is lower

Table 4A - 0.25mg Dose Batch Trend Analysis 2003 - 2006 by Year

<u>Parameter</u>	<u>Statistic</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>	<u>2006</u>
Number of Batches	-	44	35	47	44
Blend Assay(Avg)	Stability	Stable	Stable	Stable	Stable
	Ppk	2.23	4.17	2.85	2.04
	Out of Specification (%)	0	0	0	0
	Long-Term Variation (%)	46.0	53.6	26.8	55.9
Blend Assay RSD	Stability	Stable	Stable	Stable	Stable
	Ppk	1.61	2.36	1.83	1.72
	Out of Specification (%)	0	0	0	0
	Long-Term Variation (%)	0	23.9	17.3	18.7
Weight	Stability	Stable	Stable	Stable	Stable
Hardness	Stability	Stable	Stable	Stable	Stable
Thickness	Stability	Stable	Stable	Stable	Stable
Assay (% of Label)	Stability	Stable	Stable	Stable	Stable
	Ppk	6.10	2.32	2.61	1.65
	Out of Specification (%)	0	0	0	0
	Long-Term Variation (%)	4.8	17.8	7.6	27.0
Uniformity RSD	Stability	Stable	Stable	Stable	Stable
	Ppk	4.20	3.01	2.67	0.86
	Out of Specification (%)	0	0	0	4.6
	Long-Term Variation (%)	4.6	0	29.7	52.2
Weight SD	Stability	Stable	Stable	Stable	Stable
Hardness SD	Stability	Stable	Stable	Stable	Stable
Thickness SD	Stability	Stable	Stable	Stable	Stable

Table 4B - Batch Trends 0.25mg Dose 2007 - 2008 - With Year 2006 for Comparison

Parameter	Statistic	Specification	2008 APR Result	2007 APR Result	2006 APR Result
Batches	Number		20	34	44
Average Blend Assay	Average		100.2	97.7	97.7
	Range	90-110	93.1 - 104.6	93.2 - 101.6	94.8 - 100.0
	Out of Specification %		0	0	0
Blend Assay RSD	Average		1.3	1.4	1.7
	Range	< 5%	0.7 - 2.0	0.8 - 2.9	0.8 - 4.5
	Out of Specification %		0	0	0
Tablet Weight	Average		0.121	0.121	0.120
	Range	0.114 - 0.126	0.116 - 0.125	0.114 - 0.126	0.115 - 0.125
	Out of Specification %		0	0	0
Tablet Hardness	Average		4.6	4.6	4.6
	Range	2.2 - 8.0	2.8 - 6.5	3.0 - 6.8	3.0 - 6.8
	Out of Specification %		0	0	0
Tablet Thickness	Average		3.15	3.14	3.10
	Range	2.70 - 3.70	3.03 - 3.60	3.00 - 3.48	3.00 - 3.30
	Out of Specification %		0	0	0
Assay (% of Label)	Average		98.2	97.2	98.9
	Range	90 - 110	94.7 - 101.7	94.1 - 100.7	96.2 - 102.4
	Out of Specification %		0	0	0
Content Uniformity AV	Average		3.9	4.5	4.1
AV = Acceptance Value	Range	< 15%	2.1 - 7.1	2.0 - 7.1	1.5 - 8.4
	Out of Specification %		0	0	0

Table 5 - Descriptive Statistics: 0.125mg Dose Batch Averages 2003 - 2007
Blend Assay (Avg), Blend Assay RSD, Tablet Weight, Hardness, Thickness, Assay (%),
Content Uniformity

Variable	Year	N	Mean	StDev	Minimum	Maximum
Blend Assay (Avg)	2003	56	98.482	0.698	97.000	100.700
	2004	42	98.757	0.542	97.700	100.000
	2005	53	98.483	0.818	96.500	100.800
	2006	50	97.698	1.041	96.000	100.300
	2007	53	98.609	2.367	92.300	104.100
Blend Assay (RSD)	2003	56	1.8386	0.5437	0.9128	3.1762
	2004	42	1.6291	0.5041	0.8122	3.0211
	2005	53	1.7928	0.5679	0.6179	3.8855
	2006	50	1.730	0.732	0.609	3.830
	2007	53	1.4908	0.6951	0.4040	4.0434
Weight	2003	56	0.10584	0.000371	0.10500	0.10600
	2004	42	0.10524	0.000431	0.10500	0.10600
	2005	53	0.10589	0.000320	0.10500	0.10600
	2006	50	0.10582	0.000388	0.10500	0.10600
	2007	53	0.10591	0.000295	0.10500	0.10600
Hardness	2003	56	4.2982	0.1689	3.9000	4.6000
	2004	42	4.1738	0.1398	3.9000	4.5000
	2005	53	4.2962	0.1839	3.9000	4.7000
	2006	50	4.2820	0.1521	4.0000	4.7000
	2007	53	4.2434	0.2341	3.9000	4.9000
Thickness	2003	56	2.6707	0.0216	2.6300	2.7400
	2004	42	2.6824	0.0224	2.6500	2.7300
	2005	53	2.7245	0.0213	2.6900	2.7700
	2006	50	2.6998	0.0170	2.6700	2.7500
	2007	53	2.7117	0.0174	2.6700	2.7400
Assay (% Label)	2003	56	99.721	0.617	98.300	101.200
	2004	42	99.995	0.563	98.800	101.100
	2005	53	99.826	0.791	98.700	101.700
	2006	50	99.262	0.886	96.600	101.700
	2007	53	98.047	1.879	94.900	101.900
Uniformity(RSD)	2003	56	1.9661	0.4222	0.9000	3.0000
	2004	42	1.8929	0.3345	1.1000	2.6000
	2005	53	1.9755	0.4926	0.7000	3.1000
	2006	50	1.8520	0.4418	1.0000	3.1000
	2007	52	1.9361	0.6227	1.0091	3.6428

Table 6 - Descriptive Statistics: 0.25mg Dose Batch Averages for Blend Assay, Blend Uniformity RSD, Tablet Weight, Hardness, Thickness, Assay (%), and Content Uniformity

Variable	Year	N	Mean	StDev	Minimum	Maximum
Blend Assay (Avg)	2003	44	99.050	0.889	97.800	102.200
	2004	35	98.880	0.490	97.600	99.700
	2005	47	98.538	1.000	95.600	101.300
	2006	44	97.668	1.254	94.800	100.000
Blend Assay RSD	2003	44	2.0683	0.6065	0.8081	3.2356
	2004	35	1.8638	0.4427	1.2109	2.7664
	2005	47	1.7378	0.5952	0.7085	3.6961
	2006	44	1.6619	0.6464	0.7136	4.5000
Weight	2003	44	0.12030	0.000462	0.12000	0.12100
	2004	35	0.12063	0.000490	0.12000	0.12100
	2005	47	0.12038	0.000491	0.12000	0.12100
	2006	44	0.12070	0.000462	0.12000	0.12100
Hardness	2003	44	4.6545	0.4443	4.0000	5.5000
	2004	35	4.4086	0.3609	3.9000	5.5000
	2005	47	4.6553	0.3832	4.2000	5.6000
	2006	44	4.6114	0.2003	4.2000	5.2000
Thickness	2003	44	3.1614	0.0235	3.1100	3.2000
	2004	35	3.1751	0.0120	3.1400	3.1900
	2005	47	3.1591	0.0178	3.1100	3.1900
	2006	44	3.1423	0.0195	3.1000	3.1800
Assay%	2003	44	99.820	0.809	98.600	102.900
	2004	35	100.13	0.699	98.10	101.60
	2005	47	99.951	0.644	98.300	101.200
	2006	44	98.705	1.272	96.100	102.400
Content Uniformity RSD	2003	44	1.8114	0.3272	0.6000	2.6000
	2004	35	1.9600	0.4480	0.9000	3.5000
	2005	47	1.8404	0.5195	0.5000	3.4000
	2006	44	2.130	1.500	0.800	8.400

Table 7 – Batch 70924A QA Start-Up Data

Analysis	Statistic	Weight	Hardness	Thickness
	Sample Size	180	180	180
Station Homogeneity (Stability)	ANOVA (see GLM below)	No Effect	No Effect	No Effect
Capability	Ppk	1.2	1.98	3.56
	Out of Specification %	0	0	0
GLM ANOVA	Stations*	0.157	0.615	0.192
	Tablet Press*	0.284	0.098	0.158
	Location (Front vs. Rear)*	0.431	0	0.651
	Press-Location Interaction*	0.002	0.845	0.022
	Adjusted R-Square	21.60%	27.40%	7.50%
Homogeneity of Variance Press and Location Combinations*		0	0.135	0.006

*Tabled values are p-values

Table 8 – Batch 70924A QA In-Process Sampling

Analysis	Statistic	Weight	Hardness	Thickness
	Sample Size	900	450	450
Process Stability	Control Chart	Stable	Stable	Stable
Capability	Ppk	1.39	1.03	2.22
	Out of Specification %	0	0	0
GLM ANOVA	Tablet Press*	0	0.14	0
	Location (Front vs. Rear)*	0.064	0.49	0.019
	Press-Location Interaction*	0.899	0.132	0.692
	Adjusted R-Square	1.60%	0.40%	3.30%
Homogeneity of Variance*		0.181	0.000	0.000
Normal Distribution*		<.005	0.018	<.005

* Tabled value are p-values

Table 9 – Batch 70924A Operator In-Process Sampling

Analysis	Statistic	Weight	Hardness	Thickness
	Sample Size	184	552	552
Process Stability	Control Chart	Stable	Stable	Stable
Capability	Ppk	1.15	1.13	2.65
	Out of Specification %	0	0	0
GLM ANOVA	Tablet Press*	0.157	0.011	0.065
	Location (Front vs. Rear)*	0.284	0.293	0.634
	Press-Location Interaction*	0.431	0.925	0.072
	Adjusted R-Square	0.40%	0.80%	0.70%
Homogeneity of Variance*		0.612	0.000	0.000
Normal Distribution*		<.005	<.005	<.005

* Tabled Values are p-value

Table 10 – Batch 70924A QA and Operator In-Process Data

Analysis	Statistic	Weight	Hardness	Thickness
	Sample Size	274	1002	1002
Process Stability	Control Chart	Stable	Stable	Stable
Capability	Ppk	1.11	1.08	2.43
	Out of Specification %	0	0	0
GLM ANOVA	Tablet Press*	0.058	0.990	0.045
	Location (Front vs. Rear)8	0.009	0.004	0.000
	Press-Location Interaction*	0.115	0.727	0.048
	Adjusted R-Square	3.50%	0.50%	2.00%
Homogeneity of Variance*		0.097	0.099	0.067
Normal Distribution*		<.005	0.018	<.005

*Tabled value is p-value

Table 11 – Batch 70924A Short and Long-Term Process Variation

Data Source	Press	Source of Variation	Type of Variation	%Weight Variation	Weight p-value	%Hard Variation	Hard p-value	%Thick Variation	Thick p-Value
Operator In-Process	67	Time	Long-Term	13.2	0.189	19.2	0.011	3.4	0.340
		Sample+ Tablets	Short-Term	86.8		80.8		96.6	
		Total		100		100		100	
		Sample Size		90		270		270	
Operator In-Process	71	Time	Long-Term	37.9	0.004	23.4	0.003	32	0.000
		Sample+ Tablets	Short-Term	62.1		76.6		68	
		Total		100		100		100	
		Sample Size		94		282		282	
QA In-Process	67	Time	Long-Term	2.4	0.329	31.9	0	20.7	0.005
		Sample+ Tablets	Short-Term	97.6		68.1		79.3	
		Total		100		100		100	
		Sample Size		420		210		210	
QA In-Process	71	Time	Long-Term	7.9	0.048	18.3	0.021	18.2	0.029
		Sample+ Tablets	Short-Term	92.1		81.6		81.8	
		Total		100		100		100	
		Sample Size		480		240		240	

Table 12 - Tablet Content Uniformity - Actavis Batch 70924A and 484 Sampling Data

Data Source	Dose	Sample	Number of Tablets	Average	Standard Deviation	Relative Standard Deviation%
Actavis	0.125	1-AP	10	105.08	0.85	0.8
Batch 70924A	0.125	2-DIL	10	96.75	1.10	1.1
	0.125	3-Dil	10	104.43	1.32	1.3
	0.125	4-HP	6	99.00	2.10	2.1
484 Sampling	0.125	377410	10	96.75	1.88	1.9
	0.125	453913	10	97.14	1.42	1.5
	0.125	462746	10	99.36	1.74	1.8
	0.125	448881	10	100.24	1.13	1.2

Tests for Within Sample Equality of Variance and Conclusions

All Relative Standard Deviation values are within specification of 5% with a range of 0.8-2.1

0.125mg Dose - All 8 samples - $p=0.516$ -- Samples have same content uniformity

0.125mg Dose - Actavis Data - 4 Samples - $p=0.091$ -- Samples have same content uniformity

0.125mg Dose - 484 Sampling Data - 4 samples - $p=0.829$ -- Samples have same content uniformity

0.125mg Dose - Actavis vs. 484 Sampling - $p=0.614$ -- Samples have same content uniformity

Analysis of Stability Data Collected by Celsis on Behalf of UDL
Defendant's Exhibits 83 and 84
33 stability Tests Reported – Data Were Not Reported for 4 of the tests

Table 13 - Analysis of Stability Data – 0.125mg Dose – 18 Stability Tests

General Linear Model Analysis of Variance (GLM ANOVA)

Least Squares Means – Expiration Date is 18 Months

Month	----Assay----		--Dissolution--	
	Mean	SE Mean	Mean	SE Mean
3	96.71	0.4177	98.28	1.2997
6	96.50	0.4177	95.89	1.2997
9	96.88	0.4357	95.97	1.3558
12	97.23	0.4357	96.38	1.3558
18	96.82	0.4520	97.56	1.4064
24	96.10	0.4878	96.16	1.5178
36	95.48	0.9445	97.08	2.9391

Conclusion: 0.125mg Dose Product is stable with respect to Assay and Dissolution

- No significant differences among the monthly means – Assay p=0.521; Dissolution p=0.336 (GLM ANOVA)
- Linear trend over months was not statistically significant – Assay p=0.221, Dissolution p=0.820 (GLM ANOVA)

Table 14 - Analysis of Stability Data – 0.25mg Dose – 11 Stability Tests

General Linear Model Analysis of Variance (GLM ANOVA)

Least Squares Means – Expiration Dates is 18 Months

Month	----Assay----		--Dissolution--	
	Mean	SE Mean	Mean	SE Mean
3	96.75	0.5968	96.64	1.3020
6	97.58	0.6316	97.33	1.3780
9	96.63	0.5968	99.82	1.3020
12	96.89	0.6353	97.51	1.3861
18	96.92	0.6353	96.01	1.3861
24	95.92	0.6353	96.41	1.3861
36	95.48	1.4942	93.28	3.2599

Conclusion: 0.25mg Dose Product is stable with respect to Assay and Dissolution

- No significant differences among the monthly means – Assay p=0.632; Dissolution p=0.362 (GLM ANOVA)
- Linear trend over months was not statistically significant – Assay p=0.141; Dissolution p=0.198 (GLM ANOVA)

Tables 15-16
Analysis of QA Sampling and Operator Data for Batch 70836A

Table 15 - QA In-Process Sampling Batch 70836A

Analysis	Statistic	Weight	Hardness	Thickness
	Sample Size	720	360	360
Process Stability	Control Chart	Stable	Stable	Stable
Capability	Ppk	0.97	2.34	5.17
	Out of Specification %	0	0	0
GLM ANOVA	Tablet Press*	0.000	0.000	0.000
	Location (Front vs. Rear)*	0.047	0.000	0.016
	Press-Location Interaction*	0.564	0.831	0.056
	Adjusted R-Square	1.90%	9.40%	9.90%

* Tabled value are p-values

Table 16 - Operator In-Process Sampling Batch 70836A

Analysis	Statistic	Weight	Hardness	Thickness
	Sample Size	144	432	432
Process Stability	Control Chart	Stable	Stable	Stable
Capability	Ppk	1.29	2.31	6.18
	Out of Specification %	0	0	0
GLM ANOVA	Tablet Press*	0.738	0.153	0.000
	Location (Front vs. Rear)*	0.655	0.000	0.003
	Press-Location Interaction*	0.794	0.171	0.356
	Adjusted R-Square	0.00%	9.60%	13.90%

* Tabled value are p-values

Tables 17-18
Analysis of QA Sampling and Operator Data for Batch 70925A

Table 17 - QA In-Process Sampling Batch 70925A

Analysis	Statistic	Weight	Hardness	Thickness
	Sample Size	900	450	450
Process Stability	Control Chart			
Capability	Ppk	1.91	1.78	2.91
	Out of Specification %	0	0	0
GLM ANOVA	Tablet Press*	0.000	0.377	0.230
	Location (Front vs. Rear)*	0.007	0.000	0.238
	Press-Location Interaction*	0.311	0.796	0.658
	Adjusted R-Square	3.60%	2.90%	0.60%

* Tabled value are p-values

Table 18 - Operator In-Process Sampling Batch 70925A

Analysis	Statistic	Weight	Hardness	Thickness
	Sample Size	180	540	540
Process Stability	Control Chart	Stable	Stable	Stable
Capability	Ppk	1.31	1.76	4.80
	Out of Specification %	0	0	0
GLM ANOVA	Tablet Press*	0.244	0.113	0.031
	Location (Front vs. Rear)*	0.857	0.155	0.384
	Press-Location Interaction*	0.937	0.539	0.076
	Adjusted R-Square	0.00%	0.40%	1.00%

* Tabled value are p-values

Tables 19-20 - Comparison of Batches 70836A, 70924A and 70925A**Table 19 - QA Sampling Batches 70836A, 70924A and 70925A**

Analysis	Statistic	Batch	Weight	Hardness	Thickness
	Sample Size	70836A	720	360	360
		70924A	900	450	450
		70925A	900	450	450
Process Stability	Control Chart	70836A	Stable	Stable	Stable
		70924A	Stable	Stable	Stable
		70925A	Stable	Stable	Stable
Capability	Ppk	70836A	0.97	2.34	5.17
		70924A	1.39	1.03	2.22
		70925A	1.91	1.78	2.91
	Out of Specification %	70836A	0	0	0
		70924A	0	0	0
		70925A	0	0	0

Table 20 - Operator Sampling Batches 70836A, 70924A and 70925A

Analysis	Statistic	Batch	Weight	Hardness	Thickness
	Sample Size	70836A	184	552	552
		70924A	144	432	432
		70925A	180	540	540
Process Stability	Control Chart	70836A	Stable	Stable	Stable
		70924A	Stable	Stable	Stable
		70925A	Stable	Stable	Stable
Capability	Ppk	70836A	1.29	2.31	6.18
		70924A	1.15	1.10	2.65
		70925A	1.31	1.76	4.80
	Out of Specification %	70836A	0	0	0
		70924A	0	0	0
		70925A	0	0	0